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Abstract Book

Selected Abstracts of Oral/Podium Presentations and Poster Abstracts

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH • NATIONAL INSTITUTE OF MENTAL HEALTH
NIMH National Institute of Mental Health

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Selected Highlights of Oral Sessions

Tuesday, May 27, 2003

WORKSHOP 1
Complementary and Alternative Treatments: Research Challenges
9:00 am – 12:00 pm

Basic Mechanism: Nuclear Xenobiotic Receptor PXR: A Molecular Target for St. John's Wort
Steven A. Kliewer, Ph.D.
University of Texas – Southwestern Medical Center

The Pregnane X Receptor (PXR) is a member of the steroid/thyroid hormone receptor family that plays an important role in protecting the body against toxic xenobiotics. PXR is activated by a structurally diverse collection of xenobiotics including several widely used prescription drugs and hyperforin, a psychoactive constituent of the herbal antidepressant St. John's wort. PXR regulates a large set of genes including those encoding phase I and phase II enzymes and transporters, which are collectively involved in the metabolism and excretion of lipophilic substances from the body. Although PXR evolved to protect, its activation by drugs, including St. John's wort, represents the molecular basis for an important class of drug interactions in which one drug accelerates the metabolism of a second medication. In vitro PXR bioassays can now be used to predict and to prevent drug interactions such as those caused by St. John's wort.

Fishing For Efficacy: The Omega-3 Story
David Mischoulon, M.D., Ph.D.
Massachusetts General Hospital

Omega-3 fatty acids are polyunsaturated lipids derived from fish oil and vegetable sources such as flax seed oil. Recent evidence suggests effectiveness for bipolar disorder, unipolar depression, and psychotic disorders. The mechanism of action of omega-3's may involve neuronal membrane stabilization, anti-inflammatory effects, and inhibition of G-protein signal transduction. Early studies with omega-3s used doses up to 9-10g/day, but recent studies suggest benefit with as little as 1-2g/day. Investigators have recently begun comparing the efficacy of the two main omega-3 fatty acids, docosahexanoic acid (DHA) and eicosapentanoic acid (EPA), and the evidence thus far appears to support EPA as more effective than DHA. Overall, omega-3 fatty acids appear to be a well-tolerated, promising treatment for a broad range of psychiatric conditions. Further comparison between the different types of omega-3 fatty acids and placebo is needed, as well as investigation of the psychotropic mechanisms of action of the omega-3s.

Tuesday, May 27 *(continued)*

WORKSHOP 2
Enhancing Precision in Clinical Trials VI
Part 1: 9:00 am – 12:00 pm; Part 2: 1:00 pm – 5:00 pm

This all-day workshop brings together thought leaders from academia, government, and industry to discuss theoretical, methodological, and technical advances designed to enhance precision in clinical trials. The morning session will focus on Applications beginning with a presentation by John Ware, PhD., QualityMetric, on patient-based quality of life and health outcome assessment. Bernice Kuca, MA, Sepracor, will discuss diaries for sleep and functioning as used for efficacy measures in registration trials. Nina Engelhardt, Ph.D., Eli Lilly, will compare traditional versus enriched rater training techniques. The morning session will conclude with an overview by Tom Laughren, M.D., FDA, on the use of self-report ratings in clinical trials.

The afternoon session will focus on Theory with presentations from the following four speakers: David Kupfer, M.D., Western Psychiatric, presenting an update from the NIMH Conference on Assessment of Depression and Anxiety in Depression Treatment Trials; David DeBrota, M.D., Eli Lilly, discussing new self-report assessments and methodological issues in clinical trials; Cathryn Clary, M.D., Pfizer, describing methodological issues arising from the pregabalin and sertraline trials in generalized anxiety disorder; and, John Rush, M.D., University of Texas Southwestern, providing an update on study methodology and self-report from the STAR*D project.

WORKSHOP 3
Beyond Short-Term Treatment Effects:
Can We Change the Course of Illness Through Treatment?
Part 1: 9:00 am – 12:00 pm; Part 2: 1:00 pm – 5:00 pm

Long-term Treatment with Risperidone of Children with Autism
Michael Aman, Ph.D.
Ohio State University

This is a follow-up of autistic children who were participants in the Autism RUPP risperidone treatment study. All participants were initially chosen for the presence of high Irritability subscale scores ($18) on the Aberrant Behavior Checklist (ABC). Some 83 of 101 children (82.2%) were reassessed 18 months after their entry into a double-blind, placebo-controlled, 8-week trial. Measurements at entry and follow-up included the following: (a) parent interviews (Vineland Adaptive Behavior), (b) parent checklists of behavior problems, (c) parent report of participant nutritional habits, (d) vital signs and physical examination, (e) standardized assessments for extrapyrmidal symptoms (EPSs) and dyskinetic movements, (f) side effects review, (g) height and weight, (h) clinical laboratory tests and ECG, and (i) clinician CGI ratings. Follow-up assessments generally took approximately 5 to 6 hours to complete. In our analysis, we examine the following. First, we report the number of risperidone responders who remained on risperidone at follow-up. Second, we look at a variety of safety issues. Weight, EPSs, and dyskinetic symptoms are assessed in relation to cumulative exposure to risperidone. We examine prolactin, triglyceride, and cholesterol concentrations in relation to cumulative exposure to risperidone and with respect to body mass index changes. Finally, parent checklist behavior ratings, Children's Yale-Brown Obsessive Compulsive Scale scores and CGI ratings are reported in relation to medication status at follow-up and with respect to cumulative exposure to risperidone.

Tuesday, May 27 *(continued)*

WORKSHOP 3 *(continued)*
Beyond Short-Term Treatment Effects:
Can We Change the Course of Illness Through Treatment?
Part 1: 9:00 am – 12:00 pm; Part 2: 1:30 pm – 5:00 pm

Follow-up in the Multimodal Treatment Study of Children with ADHD (MTA)
L. Eugene Arnold, M.D.
Ohio State University

Despite hundreds of well-controlled acute studies of attention-deficit/hyperactivity disorder (ADHD) and its treatment, there are few long-term outcome studies and even fewer focused on treatment effects. The 6-site NIMH Multimodal Treatment Study of Children with Attention-Deficit Hyperactivity Disorder ("The MTA") treated children age 7-9 with combined-type ADHD for 14 months in 4 randomly assigned groups, then continued to follow their progress periodically. The 4 original assigned treatments were careful medication management (MedMgt), intensive behavioral treatment (Beh), their combination (Comb), and routine community treatment as a comparison group (CC). 2/3 of the latter received medication from community physicians, but inconsistently, at lower doses, and less frequently during the day. At 14 months, Comb and MedMgt were not significantly different, but both were significantly better than either Beh or CC, which were not significantly different from each other, for ADHD and oppositional-defiant (ODD) symptoms. This superiority persisted at 24-month follow-up 10 months after cessation of MTA-administered treatment, but with a smaller effect size as the treatment was taken over by community providers.

The original randomized group means appeared to have started converging as the treatment distinctions became blurred. The convergence in outcome appeared due to deterioration in the two groups (Comb and MedMgt) that had shown the most benefit at 14 months. The Beh and CC groups maintained their 14-month level of improvement through 24 months even though no further behavioral treatment was provided after 14 months (parents had been trained to continue Beh on their own). Medication during the 10-month interim and in the 30 days prior to the 24-month assessment significantly moderated the 24-month outcome: continued medication and newly started medication had a significant positive effect while discontinuation of medication was associated with deterioration. The percent medication for all 4 randomly assigned groups prior to study entry was 26-34%. At 14 months the two groups randomly assigned to medication (Comb and MedMgt) had 85-87% medicated, Beh had 26% medicated (nonprotocol), and CC 67% medicated. At 24 months, the percent use of medication had begun converging in parallel with the outcome measures, being 70%, 72%, 38%, and 62%, respectively. The MTA sample is currently being systematically re-evaluated every 2 years in an attempt to assess the distal effects of treatment on symptoms and functioning.

Detecting distal effects on low baserate disorders: What can we learn from prevention research?
C Hendricks Brown
University of South Florida

We test most of our interventions, whether they are treatments for existing disorders or preventive interventions that precede a disorder, on proximal effects. Yet the long-term effect of interventions may far outweigh short-term gains. We discuss recent methodologic advances called General Growth Mixture Modeling (GGMM) that allow us to connect these proximal and distal effects in growth models. These models use discrete mixtures to allow for the intervention to have varying impact within a target population. These models are then applied to examining the impact of a preventive intervention in first grade on the course of aggressive behavior and a diagnosis of antisocial personality disorder in young

adulthood. In a second application we discuss combining data from multiple randomized trials to examine whether they have long-term impact on reducing or delaying the rate of completed suicide. While the rate of suicide in the United States is far too high, its rate is far lower than that of many outcomes we intend to study. This "low baserate" for suicide introduces challenging problems for the design and analysis of long-term effects. We present new methods specifically relevant to suicide prevention.

Are There Persistent Effects of Cognitive-Behavioral Therapy in Depressed Adolescents?
Gregory Clarke, Ph.D.
Kaiser Permanente Research Foundation

Cognitive behavioral (CB) interventions have a strong evidence base for depression in adults and adolescents. However, most outcome trials focus on acute response, with less known about persistence of effects over time. This presentation will review long-term outcomes for depressed adolescents from six CB treatment trials and two CB prevention trials, all with post-intervention follow-up of at least two years. In general, treatment and prevention acute effects begin to fade by 1 to 2 years post-intervention, although there was still a detectable advantage of the CB *prevention* program at two-years follow-up. The overall pattern of diminished effects over time suggests the need for periodic booster or maintenance sessions.

A strikingly different pattern of results is emerging from our ongoing adolescent depression effectiveness trial (n=152), comparing SSRIs with and without CBT in the context of usual care in an HMO. First, we have been unable to detect acute treatment CBT advantages, in part because of very high (~ 80%) acute *recovery* rates in the SSRI-only arm of the study. Interestingly, the advantages of CBT are just beginning to *emerge* at 12 months post-acute treatment. Several measures indicate an increase in depression symptomatology in the SSRI-only condition, compared to continuing low depression symptoms in the CBT+SSRI arm. This suggests that CBT adjunctive to SSRIs may be most beneficial for *preventing* future depression recurrence or relapse—similar to the long-term advantages of CBT found in the adult depression literature.

Is there a European regulatory perspective to studying long-term pharmacological effects in naturalistic settings?
Joerg Fegert, M.D.,
University of Ulm

Though less dramatic than in the U.S., the use of psychotropic medications among children has increased also in Europe. In spite of expanded research in child psychopharmacology, concerns about the safety of these medications during development remain. Clinical trials have provided data on the short-term effects of certain medications in children, but are limited by the brief duration of assessment, the relatively small sample size, and the questionable representativeness of the subjects entering controlled experimentation. The use psychotropic medications in practice settings can offer an opportunity to identify possible associations between safety relevant outcomes and drug exposure. Naturalistic data are

limited in their capacity to establish causality, but, because of the large sample size, can be sensitive to detection of a possible signal. This potential has remained, however, in large part unfulfilled due to the lack of a systematic plan of data collection. Possible approaches to studying pharmacological effects in children in the community will be discussed in the light of the most recent regulatory perspective in Europe.

Stimulant Medication and Risk of Substance Abuse
Lily Hechtman, M.D., F.R.C.P.
McGill University, Montreal Children's Hospital

Concerns about the link between stimulant medication in childhood and later risk of substance abuse come from two main sources. First, animal studies, which suggest sensitization and cross sensitization of animals by stimulants to cocaine and morphine and vise versa. Second, the incidence of substance abuse is higher in adolescents and adults with ADHD than matched controls. The presentation will review animal and long-term prospective follow-up studies to address this important question. Most studies indicate that stimulant treatment in childhood does not increase the later risk of substance abuse if comorbid Conduct Disorder is controlled for. Some studies suggest that such treatment may be protective against future substance abuse.

Childhood Methylphenidate (MPH) and Substance Involvement 30 Years Later: Methodological Considerations
Jan Loney, Ph.D.
University of Iowa

Data are drawn from a 32-year longitudinal study of 324 boys who were referred to a psychiatric clinic as children for diagnosis and treatment of the constellation of problems that is now called Attention-Deficit/Hyperactivity Disorder (ADHD). The boys, their not-ADHD full brothers, and classmate controls were evaluated during adolescence and at ages 21 to 23. Currently, they are all being comprehensively evaluated between 35 and 45 years of age. At ages 21-23, participants who had been treated with methylphenidate (MPH) as children reported significantly fewer diagnoses of alcoholism and less involvement with tobacco, non-medical stimulants, glue, and opiates than did subjects who had not been treated with MPH (Loney, Kramer, & Salisbury, 2002). Within the MPH-treated group, longer stimulant treatment, higher doses of MPH, and less severe childhood aggression and inattention-overactivity were all associated with better non-substance outcomes at ages 21-23 (Paternite, Loney, Salisbury, & Whaley, 1999). This presentation will extend the analyses of medicated subjects: (a) to identify the childhood predictors of alcoholism and involvement with selected other substances at ages 21-23; and (b) to describe lifetime drug and alcohol use among the first 50 medicated individuals who have been evaluated at ages 35 to 45. It will also address some of the problems inherent in studying the long-term outcomes of stimulant treatment, and the conclusions that can and cannot be drawn using various available designs.

Tuesday, May 27 *(continued)*

WORKSHOP 3 *(continued)*
Beyond Short-Term Treatment Effects:
Can We Change the Course of Illness Through Treatment?
Part 1: 9:00 am – 12:00 pm; Part 2: 1:30 pm – 5:00 pm

The Effect of Stimulant Medication on Outcomes of Adolescents and Young Adults with ADHD
William E. Pelham, Jr., Ph.D.
State University of New York at Buffalo

Probands (N=358) were recruited as adolescents and young adults from a pool of 516 children diagnosed with ADHD at the WPIC ADHD Program between 1987 and 1996. Ninety percent of the probands were in their elementary school-aged years (ages 5 to 12) at intake, and between the ages of 11 and 22 at first follow-up interview.. Participating and nonparticipating probands were compared on multiple measures and were slightly different on only one of 14 measures. Comorbid disorders at childhood were frequent and included other disruptive behavior disorders and internalizing disorders. Comparison subjects were 240 demographically similar and adolescents and young adults without ADHD matched with probands on age, gender, parental education, and ethnicity. Extensive information was available from childhood, including history at intake, structured diagnostic interviews, standardized parent and teacher rating scales, and observational data in peer and classroom settings in a summer treatment program. Annual interviews were conducted at follow up. Information gathered included the following domains: psychopathology (e.g., SCID), academic functioning (e.g., school records, IQ, achievement), social functioning (e.g., interpersonal relationships), family functioning (e.g., parent-proband relationships), vocational adjustment (e.g., job status, job changes), substance use (e.g., Q-F, diagnostic status), psychophysiology, and treatment history (e.g., medication chronology). Most subjects had taken stimulant medication, with a wide range of length of use and a mean of 5 years. Analyses focused on lifetime use of prescribed stimulant medication as a predictor of adolescent and young adult functioning in the domains noted above, controlling for a number of child variables.

Growth Patterns of Children with Attention Deficit Hyperactivity Disorder who Receive Long-Term Treatment with Stimulant Medication
James Swanson, Ph.D.
University of California Irvine

Since the 1970's, cross-sectional and short-term follow-up studies have been reported to evaluate the possible effects of extended use of stimulant medications on the growth velocity of children with attention deficit hyperactivity disorder (ADHD). Reviews of these studies suggest small growth suppression effects on both height and weight velocities that are transitory, with no long-term growth suppression. However, small samples and methodological issues make it difficult to draw a firm conclusion based on the published studies. We report on the large sample of 579 children who entered the Multimodal Treatment Study of ADHD (MTA) when 7-9 years of age and were randomly assigned to receive one of 4 different treatment strategies (behavior therapy, medication management, combination of behavior therapy and medication management, and community treatment) for 14 months. These children are now in a prospective naturalistic follow-up, with systematic annual or biannual assessments. We will discuss our methods for evaluation of the growth curves of these children with respect to assigned treatment (in the 4 randomly assigned MTA groups) and actual treatment (in naturalistic subgroups based on treatment decisions over time), with special focus on the growth velocity in the extreme but self-selected subgroups with no exposure or continuous exposure to stimulant medications over long periods of time.

TREATMENT DEVELOPMENT SESSION 1
Pharamcogenetics of Mood and Anxiety Disorders
9:00 am – 11:00 am

Tackling The Complex Genetics of Pharmacogenomics
Francis J. McMahon, M.D.

Pharmacogenomic studies offer great promise for improved treatment of psychiatric disorders. The challenges facing pharmacogenomics are very similar to those facing most other studies of complex genetic traits in humans. What is the best approach to ascertaiment and phenotype definition? How does one achieve optimal statistical power? In what context should the results of pharmacogenomic studies be interpreted? This talk will review these and other principles and methods of complex human genetics and their application to pharmacogenomics in psychiatry.

Pharmacogenetics of Mood Stabilization In Bipolar Disorder
Martin Alda, MD, FCRPC. Department of Psychiatry, Dalhousie University, Halifax, Canada

Bipolar illness (BD) is likely a multifactorial condition comprising various disorders of mood regulation. Convergent evidence suggests that individual subtypes of BD can be defined along the lines of outcome of prophylactic treatment. Although the response to mood stabilizers is not entirely specific, responders to certain drugs may be similar to each other clinically and they often do poorly on other treatments. For instance, the response to lithium has been associated with clinical picture of typical BD, and strong family history of BD (often responsive to lithium as well). In comparison, responders to lamotrigine show high rates of co-morbid anxiety, family history of panic attacks. The pharmacological dissection of BD can be used for defining homogeneous subtypes for gene mapping studies, to search for genetic polymorphisms associated with the response. New methods of gene-expression analysis are a promising way to identify molecular targets for mood stabilizers as well. In this presentation, we will review the factors relevant for definition of lithium response as well as main clinical and molecular findings in lithium responsive BD.

TREATMENT DEVELOPMENT SESSION 2
New Approaches in Drug Discovery
1:00 pm – 3:00 pm

Gene-Based Target Identification for Schizophrenia, Depression, and Bipolar Disease
C. Anthony Altar, Ph.D.
Psychiatric Genomics, Inc.

Psychiatric illnesses involve a complex interaction of genetic and environmental influences. These influences on gene expression can be measured by the microarray analysis of brain tissue from patients and normal controls, and from human cells or brains from rodents following exposure to psychiatric drugs. Targets for developing improved mood stabilizers were identified from a "drug signature" of genes that changed in human neuron cultures exposed to lithium, carbamazepine, and valproate, but not to the antiepileptic drug dilantin. Most changes were validated with 2 microarray platforms, dose-response curves using RT-PCR, and our cell-based multi-parameter high throughput screen^{SM} (MPHTS^{SM}). These genes, their inclusion in the MPHTS^{SM} system to discover high-potency hits, and plans for proof-of-principle studies in our bipolar program will also be described. As an example of antidepressant target discovery, rats were exposed to electroconvulsive seizures (ECS) to model the treatment of choice for drug-

resistant depression. ECS altered over 140 genes, including those for neuropeptide Y, TRH, and glutamate/NMDA and at least 30 within distinct signaling pathways for BDNF/MAP kinase, cAMP, arachidonic acid, and neurogenesis. Many of these targets were validated by RT-PCR, their roles in psychiatric disease, and responses to antidepressant drugs. The "disease signature" of gene changes in psychiatric disease is illustrated for schizophrenia, for which gene targets clustering in specific biochemical pathways have been identified with dissected tissues and laser-captured hippocampal neurons, and some of which were found to overlap with the drug signature of gene changes in animals exposed to antipsychotic drugs.

Aptamers therapeutics: A novel class of nucleic acid drugs
Errol DeSouza, Ph.D.
Archemix Corp.

Archemix develops aptamer-based biotherapeutics to treat a range of human diseases. Aptamers are macromolecules composed of nucleic acids, such as RNA or DNA, that bind tightly to a specific molecular target. Aptamers, the nucleic acid equivalent of antibodies, inhibit the biological activity of targets they bind. They thus directly compete with monoclonal antibodies as potential therapeutics in disease areas where target inactivation produces an appropriate patient response. In many ways, aptamers offer specific competitive advantages over monoclonal antibodies. Therapeutic aptamers are derived by an entirely *in vitro* process from combinatorial libraries of modified oligonucleotides from which selected leads are converted into serum-stabilized agents. Aptamers bind their targets with exquisite specificity and high affinity. The therapeutic potential of aptamer-based drugs is supported through a diverse range of *in vivo* efficacy studies in animal models of disease and through results from recent human clinical trials. Aptamer therapeutics have not exhibited significant toxicity or immunogenicity. Aptamers are synthesized through scalable chemical processes at manufacturing costs that compete with monoclonal antibodies.

Aptamers also augment small molecule drug discovery efforts. They are used as affinity ligands in high throughput screening and in protein quantification and identification. Importantly, aptamers are used as agents in either intracellular or extracellular protein-level target validation studies; the intent of which is to mimic the pharmacology of small molecule agents in animal models of human disease. Aptamers are uniquely versatile validation and therapeutic development agents in the pharmaceutical armamentarium.

Screening the Receptorome Reveals Unexpected Targets for Drug Discovery
Bryan L Roth, Ph.D.
Case Western Reserve University Medical School

G-protein coupled receptors (GPCR's), ligand-gated ion channels and neurotransmitter transporters represent the proximal molecular targets responsible for the actions of the vast majority of psychoactive compounds. This subset of the genome which contains all of the receptors has been termed the

TREATMENT DEVELOPMENT SESSION 2 (continued)
New Approaches in Drug Discovery
1:00 pm – 3:00 pm

'receptorome' (Sheffler and Roth, TiPS, 2003). The number of molecular targets in the receptorome is immense with GPCR's being the largest group with at least 800 members. Via the resources of the NIMH Psychoactive Drug Screening Program we have devised two approaches to screen the receptorome to discover the proximal molecular targets responsible for drug actions. Our first approach, an *in silico* one, is to provide a web-based interface for mining information regarding drug interaction sites (see http://pdsp.cwru.edu/pdsp.asp). Currently, we have compiled >22,000 receptor affinity values encompassing >350 distinct molecular targets. We also provide physical screening of new chemical entities at an expanding number of human cloned molecular targets and have nearly 100 cloned GPCRs and a large number of cloned ion channels and transporters available for screening. I will also show how this approach has been used to predict serious toxicities early in pre-clinical testing. I will also demonstrate how this approach has been used to uncover new molecular targets for psychotherapeutic drug discovery efforts.

WORKSHOP 4
Subject Diversity in Clinical Trials: Is Recruitment Enough?
2:00 pm – 5:00 pm

The importance of ethnic diversity in psychopharmacological studies and clinical trials is now well established. Despite the scientific and clinical importance ethnic minorities are still underrepresented in clinical trials. Clearly current recruitment efforts are inadequate. This workshop will address the issue of effective recruitment, retention efforts, and protocol adherence. Factors that contribute to poor recruitment also affect every element of the clinical trial, leading to limited databases, and inadequate information for generalization.

Dorothy on the Yellow Brick Road: Innovation, Infrastructure and Divsersity in Clinical Trials
Keh-Ming Lin, MD
Harbor-UCLA Research and Education Institute

Recruitment indeed is one of the most, if not the most, crucial and challenging aspects of any successful clinical research endeavors. Difficulties in recruiting "minority" participants for such studies have received increasing attention in recent years, and policies and strategic plans have been formulated to address such discrepancies. Although these efforts are of utmost importance and should be implemented to the fullest extent, it is at the same time crucial that the field not limit its energy and attention merely on recruitment issues. We should not just aim at achieving "representation." Even more importantly, we should critically examine all issues that are essential for the understanding of questions at hand for any particular population being examined. The goals and strategies for participant recruitment should be determined by the purpose of the study. Thus, recruitment issues involving diverse groups should be included in all components of any research project, ranging from the formulation of hypotheses, the selection of study approaches, research instruments and measurement methods, the design of statistical analysis and data interpretation, as well as plans for publications and information dissemination. In addition to instilling "diversity" into clinical research in a meaningful ways, we also need to critically examine approaches that facilitate the participation of subjects from diverse backgrounds; establish

infrastructures enabling the research community to effectively address these issues (e.g., Howard-NIMH program); examine the relationships between researchers and "minority" communities, and ways to establish/strengthen them; clarify ethical issues surrounding research involving diverse populations (e.g., racial profiling; definition of ethnicity).

Beyond Tuskegee: Recruiting Ethnic Minorities with an HBCU-NIMH Collaboration
Tanya N. Alim, M.D.
Howard University

Because NIMH had few ethnic minorities in intramural research and Howard's department of psychiatry at that time had limited research involvement, a collaboration was established between the NIMH Mood and Anxiety intramural program and this Historically Black College and University. Initially Howard was to recruit subjects for NIMH protocols to be done first at the clinical center in Bethesda and later at Howard. Howard University researchers would also begin developing their own protocols for research to be done solely at Howard. Barriers to implementation will be discussed including administrative issues, human subject issues, perception of NIMH, difficulties to publicizing in the local community, and patient related personal issues. Nevertheless many protocols were approved and implemented, NIMH and Howard investigators worked cooperatively at each site, and some protocols were developed and implemented primarily at Howard.

Special Issues for the Recruitment, Retention, and Assessment of Older People with Psychotic Disorders in Clinical Trials
Jonathan P. Lacro, Pharm.D.
San Diego Healthcare System and University of California

While there will be a general increase in the number of older adults in the general population, even more striking will be the increase of older adults with psychiatric disorders. Hence, there is an important need to include older adults in clinical trials. The FDA's new Geriatric Rule warrants studies of psychotropic drugs focused on elderly patients. There are special issues involved in recruitment, assessment, and retention of older psychiatric patients in clinical trials. These include physical comorbidity, cognitive impairment, polypharmacy, drug interactions, increased risk of many side effects, psychosocial isolation, scarcity of assessment instruments validated in elderly populations, etc.

Our group has been conducting interventions studies in older patients with schizophrenia and other psychotic disorders for more than a decade. In this presentation we will discuss the strategies that we have found to be successful. The most effective strategies for recruitment of elderly patients are often different from those that are useful in younger adults. For example, elderly patients generally suffer from greater levels of physical comorbidity than younger adults, thus protocol modifications such as relaxing medical exclusionary criteria or providing transportation may be necessary to recruit and retain research participants. Administration of research assessments needs to be tailored to the abilities and limitations of older people. Thus, the frequency and duration of research assessments should be appropriate to older persons. For ethnic minorities, we utilize bilingual staff and have translated several of our assessments. Other relevant issues will be presented.

Tuesday, May 27 *(continued)*

WORKSHOP 4
Subject Diversity in Clinical Trials: Is Recruitment Enough? (continued)
2:00 pm – 5:00 pm

Subject Diversity in Clinical Trials: From Schizophrenia to Refugee Populations
David C. Henderson, M.D.
Massachusetts General Hospital

Scientific findings, whether biomedical or behavioral, may not be appropriate and applicable to ethnic minority populations unless they are adequately represented as study participants. Moreover, the need to involve greater numbers of ethnic minorities is quite urgent due to the poor morbidity and mortality outcomes associated with ethnic minority group membership. Investigators in population-based and clinical research may need to identify and recruit research participants from community settings in which little is known by investigators of the dynamics and day-to-day needs of the community. Rigorous research on the best methods for recruiting and retaining minorities is still lacking. Additionally, little is known about why research subjects withdraw consent to participate in research and whether attrition is influenced by ethnicity or other factors.

It is essential for investigators to be cognizant of previous violations and abuses of ethics and human rights. If there are cultural and environmental differences, it is absolutely crucial that researchers approach recruitment of minority groups with cultural competence and cultural sensitivity. Clinical trials must also be designed to minimize adverse events and side effects with the knowledge of differences in metabolism, lifestyle factors and diet. An understanding of the factors that influence research participation (eg, type of incentives, and schedule of payment as well as type of stationery and stamps used) is needed.

Having a community-based advisory committee, school district committee, or community center or association and an experienced recruiter or a community recruiter is essential. However, bringing someone in “to deliver” a population is not adequate, may be harmful and may lead to further the mistrust of the health care system by many minority groups. The long-term investment in minority researchers/investigators is essential. Study recruiters often face unacknowledged expectations and job pressures as they attempt to meet recruitment goals. The pressure for recruitment may lead to protocol violations, enrolling inappropriate subjects and coercion.

Elements that need to be adequately addressed include the researchers' involvement with the community in which the participants live, a tracking system to assess recruitment efforts, flexibility in the methods of recruitment, and adequate resources in time, money and personnel. Researchers must take the time to invest in the community, including validating the rating scales in the population. Budgets should reflect the additional resources needed to develop an appropriate recruitment strategy for minority groups. Researches, must also expect the recruitment period will be longer.

Data and examples from clinical trials in schizophrenia and studies in refugee populations will be discussed.

Tuesday, May 27 *(continued)*

TREATMENT DEVELOPMENT SESSION 3
MATRICS: Cognition in Schizophrenia Initiative
3:30 pm - 5:00 pm

NIMH Treatment Development for Cognition in Schizophrenia: Rationale and Strategy
Wayne S. Fenton, M.D.
National Institute of Mental Health

Although the delusions and hallucinations of schizophrenia are often treated effectively by available medications, research indicates that impairments in cognition (memory, planning, abstract thinking) are most associated with disability in this illness. Unfortunately, available medicines do little to reverse this aspect of schizophrenia. To address this problem, NIMH has launched a Schizophrenia Treatment Development Initiative focused on both developing new drug treatments to remedy cognitive impairments. With the cooperation of the FDA, this initiative will develop standard measures and methods to test new drugs that target cognition in schizophrenia in order to provide the pharmaceutical industry with guideline for drug registration and hence, enhanced incentives to invest in developing treatments for this aspect of schizophrenia. To jumpstart this effort, in FY 2004 NIMH will establish a new clinical trials network focused on collaborating with industry to identify and testing new agents for cognition in schizophrenia.

Wednesday, May 28, 2003

PLENARY SESSION
Treatment and Preventive Interventions Research: From Laboratory through Clinical Trial to Practice
10:00am – 12:15 pm

Drug Development for Mental Illness in the 21st Century
Edward M. Scolnick, M.D.

The talk will discuss how medicines for various medical illnesses have been discovered. The process will be compared to the way most medicines for severe mental illness have been discovered. The scientific changes that are taking place in several diseases will be covered and the impact that this is having on the prospect for new medicines for severe mental illness. A model for how the research, development, and clinical trial system could work in the future will also be discussed.

Wednesday, May 28, 2003

PANEL 1
Improving the Clinical Relevance of Maintenance Designs in Bipolar Disorder
2:15 pm – 4:15 pm

Working in a Complex Environment: The Multiple Challenges in Studying Psychosocial Treatments for Bipolar Disorder

Ellen Frank, Ph.D.
Western Psychiatric Institute and Clinic

Bipolar disorder, because of the marked intra- and inter-individual variability of its course, is a difficult disorder to study empirically. Regardless of the focus of the study, it presents major research design, conduct, and analysis challenges. These challenges are only magnified when the purpose of the investigation is to establish the efficacy of an adjunctive psychosocial treatment used in combination with pharmacotherapy. This presentation will describe the array of research design, conduct, analysis and interpretation decisions that investigators studying group, family and individual psychosocial interventions for bipolar disorder most confront and how these issues have been resolved in several large ongoing and recently completed trials.

PANEL 2
Integration of Neurobiological Methods into Late-Life Clinical Trials
2:15 pm – 3:45 pm

Depression in the elderly is a clinically and neurobiologically heterogeneous disorder. The clinical management of geriatric depressed patients is complicated by age-related changes in cognition, neurochemical function and drug metabolism, and by co-morbid medical illnesses, in addition to neurodegenerative and cerebrovascular disease processes. The response to antidepressant treatment in geriatric depressed patients is delayed and highly variable. Even though there are effective antidepressant agents available, some patients are still refractory to treatment. The incorporation of neurobiologic methods into clinical trials and the conduct of novel intervention studies to accelerate or augment the antidepressant response represent potentially powerful approaches for evaluating the pathophysiology of geriatric depression and for designing more effective treatments. This session will focus on how clinical trials can serve as a platform to further not only our understanding of the factors that contribute to the heterogeneity of drug response, but of the pathophysiology of geriatric depression.

Integration of Neurobiologic Methods into Late-Life Clinical Trials: Role of Structural Neuroimaging
David C. Steffens, M.D., M.H.S.
Duke University Medical Center

Neuroimaging is playing an increasingly important role in neuropsychiatric research. Structural brain changes on magnetic resonance imaging (MRI) have been associated with development of late life mood disorders. The presence of hyperintense areas in deep white matter and subcortical gray matter, thought to vascular in nature, have led investigators to term the depression associated with these changes "vascular depression." Treatment outcomes associated with vascular vs nonvascular depression will be reviewed. In addition, other structural changes, specifically volumetric studies of the structures thought to be important in mood disorders and their outcomes will be discussed.

TREATMENT DEVELOPMENT SESSION 5
Innovative, Mechanism Based Treatment Strategies in Anxiety and Depression
4:00 pm – 6:00 pm

Replication of The Efficacy and Tolerability Of Substance P Antagonists In Patients With Major Depression
William A. Ball, M.D., Ph.D.
Merck Research Laboratories

Data from a past clinical study with MK-0869 suggested that Substance P (NK1 receptor) Antagonists (SPAs) would provide a unique mechanism of antidepressant activity. In order to generalize this finding, we tested the efficacy and safety of another selective substance P antagonist, L-759274, in outpatients with a diagnosis of major depression (MDD) with melancholic features.

Patients were male or female, aged 18-60 in this randomized, double blind placebo-controlled study. Patients scoring 25 points on the total of the first 17 items of the 21-item Hamilton Depression Scale (HAMD), and 4 (moderately ill) on the Clinical Global Severity Scale (CGI-S) were randomized to L-759274 40 mg once daily in the evening (n=66), or matching placebo (n=62) for 6 weeks.

Treatment with L-759274 40 mg was associated with an improvement (mean decrease from baseline) in HAMD-17 total score of 10.7 points, compared with the mean 7.8 point improvement in patients receiving placebo ($p<0.009$). Mean scores on the Clinical Global Improvement scale (CGI-I) improved significantly in favor of L-759274 40 mg by the end of the trial ($p<0.009$). Mean scores for item 1 of the HAMD-17 (depressed mood) also improved to a greater extent in the active group compared with the placebo group (0.3 points, $p<0.058$). In this study, L-759274 40 mg was generally safe and well tolerated. The incidences of sexual side effects and GI symptoms were similar to those observed in patients receiving placebo.

Two different highly selective substance P antagonists (MK-0869 and L-759274) have been observed to be antidepressant. Thus, substance P antagonism is a bona fide and generally well tolerated antidepressant mechanism.

Acute Treatment of Bipolar Depression with an Olanzapine:Fluoxetine Combination
Gary D. Tollefson, M.D., Ph.D.

Despite the longer time that bipolar patients spend in the depressive phase, relatively few controlled studies have examined treatment strategies for bipolar depression. In the present study we hypothesized that an augmentation strategy coupling the selective serotonin uptake inhibitor fluoxetine with the atypical psychotropic olanzapine, might be associated with a more rapid induction of antidepressant activity in bipolar 1 disorder. This was based on literature suggesting that combination strategies might build on monoamine uptake inhibition through the addition of other pharmacologic mechanisms in a double-blind, eight-week, randomized controlled trial. A total of 833 randomized adult patients with bipolar I depression with a Montgomery-Asberg Depression Rating Scale (MADRS) score $\geq$20 were randomly assigned. Beginning at week 1, both the olanzapine and olanzapine/fluoxetine groups showed statistically significant improvement in depressive symptoms compared to the placebo group throughout the study (P's <.001). The olanzapine/fluoxetine group also showed statistically greater improvement than the olanzapine group at weeks 4 through 8. Remission criteria were met by 24.5% of placebo

patients, 32.8% of olanzapine patients, and 48.8% of olanzapine/fluoxetine patients. Treatment-emergent mania did not differ among groups (placebo 6.7%, olanzapine 5.7%, olanzapine/fluoxetine 6.4%). Adverse events for olanzapine/fluoxetine were similar to those of olanzapine. Results suggest that olanzapine/fluoxetine demonstrates a very favorable profile in the treatment of bipolar I depression.

Clinical Trials of Mifepristone for Psychotic Major Depression (PMD)

Joseph K. Belanoff, M.D.
Corcept Therapeutics

The rationale for treating patients with psychotic major depression (PMD) with glucocorticoid receptor (GR) antagonist is explained. Data from four clinical studies where mifepristone was used to rapidly ameliorate symptoms of PMD will be described:

1. A Double-Blind Placebo-Controlled Crossover Study;
2. An Open Label Variable Dose Study;
3. A Double-Blind Placebo Controlled "Add-On" Study'
4. An Open-Label Retreatment Study.

The Role of Glutamate Antagonist

K. Ranga R. Krishnan, M.D.
Duke University Medical Center

Existing pharmacological approaches for treating anxiety consist of benzodiazepines acting via facilitation of GABAergic neurotransmission; buspirone, a 5-HT_{1A} partial agonist; and venlafaxine and paroxetine, a mixed noradrenergic-serotonergic uptake inhibitor and a serotonergic uptake inhibitor, respectively. These treatments have significant limitations, such as sedation, cognitive impairment, dependence/withdrawal syndromes (benzodiazepines), or sexual dysfunction, sleep dysfunction, or activating events (paroxetine, venlafaxine). An agent with a more specific role in ameliorating the symptoms of anxiety without these features might have greater utility. *L*-glutamate (glutamate) is present throughout the central nervous system (CNS) and plays a major role as an excitatory neurotransmitter in most CNS processes. Glutamate-stimulated, fast synaptic transmission is modulated via G-protein-coupled (metabotropic) receptors (mGlu). The mGlu2 receptors are expressed (mGlu2 mRNA) primarily in the brain's limbic structures. These areas (in particular, the amygdaloid nuclei) are thought to play an important role in the somatic expression of fear via the brain stem/spinal cord and to be an important site of action of anxiolytic drugs.

Wednesday, May 28 *(continued)*

PANEL 3
Growing Role of Proof of Concepts in CNS Drug Development
4:30 pm – 6:00 pm

CNS Disease Modelling in Human Subjects
Rémy Luthringer, Ph.D.
Forenap

It is well known that CNS compounds are often failing in clinical development, because behavioural animal models are not predictive enough, but also because the Phase I part is not documenting mechanism of action and early evidence of effectiveness.

Proof Of Concept (POC) is now more and more used in the target patient population. This later approach shows some limitations, because psychiatric syndromes are frequently heterogeneous and because comorbidity is frequent (i.e. anxiety during affective disorders).

An alternative could be to develop models (provocation of core signs / symptoms measured with functional markers like brain mapping techniques) in healthy volunteers. State of art in this research field will be given for different neuropsychiatric fields (i.e. ageing; depression; anxiety; schizophrenia)

Thursday, May 29, 2003

PANEL 4
Psychopharmacology and Reproductive Transitions
9:00 am – 12:00 pm

Weight-Gain Inducing Psychotropic Medications, Gender, and Potential Pharmacologic Strategies
Barbara Gracious, M.D.
University of Rochester

Weight gain due to psychotropic medication is increasingly recognized as a serious problem for our patients who have no other viable options for non-weight inducing effective pharmacologic treatment. Potential consequences of weight gain include not only insulin resistance, but also a constellation of findings that are collectively known as the metabolic syndrome, which increases risk for diabetes as well as cardiovascular disease leading to multiple systemic organ impairment. This talk will review the data to date on this cause of weight gain as well as gender differences in weight gain and subsequent systemic effects. Potential novel pharmacologic options for management will be discussed.

PANEL 4 *(continued)*
Psychopharmacology and Reproductive Transitions
9:00 am – 12:00 pm

Testosterone Decline in Aging Men: Does "Andropause" Exist?
Stuart N. Seidman, M.D.
Columbia University

In contrast to women, men do not experience a sudden cessation of gonadal function comparable to menopause. However, there is a progressive decline in hypothalamic-pituitary-gonadal (HPG) function in aging men: testosterone (T) levels decline and there is a loss of circadian rhythm of T secretion. By age 75, mean plasma T levels have decreased 35% compared to young adults, and more than 25% of men this age are clinically hypogonadal. Age-related hypogonadism, which has been termed "andropause," is thought to be responsible for a variety of symptoms experienced by elderly men, including reduced muscle and bone mass, sexual dysfunction, depression, fatigue, and irritability. However, it has been difficult to establish correlations between these symptoms and plasma T levels. Studies of T replacement have documented some symptom relief (e.g., improved muscle strength and bone mineral density), yet studies to date on the specific relation between depression and T level have been methodologically flawed. Data is presented from systematic clinical and epidemiological studies with bearing on this relation: 1) placebo-controlled clinical trials of T replacement in men with major depressive disorder (MDD); and 2) population-based assessments of the relation between T level, genetic factors, and depression in elderly men. Results suggest that age-related HPG hypofunction may have particular etiologic importance in late-onset male dysthymia.

Perimenopause, Mood, and Estrogens
Claudio N. Soares, M.D., Ph.D.
Massachusetts General Hospital

The menopausal transition has been associated with heightened prevalence and exacerbation of underlying psychiatric illness, particularly depressive symptoms. It has been speculated that sex steroids exert a significant modulation of brain functioning, possibly through interactions with various neurotransmitter systems. It is therefore intuitive that abrupt alterations of these hormones would interfere with mood and behavior. On the other hand, accumulating data suggest that hormonal interventions may also promote relief or even remission of depressive symptoms.

This presentation will critically review recent data on the complex relationships between sex hormones and mood during the perimenopause. The prevalence and risk factors for recurrent /new onset of depression during the perimenopause (The Harvard Study of Moods and Cycles) will be discussed. Also, preliminary but promising data on the use of estrogens as an antidepressant strategy (monotherapy or augmenting agent) for perimenopausal and postmenopausal women with depression will be reviewed.

TREATMENT DEVELOPMENT SESSION 6
Cognition Across Diagnostic Entities: Shared and Unique Aspects of Cognitive Impairment Across Depression, Bipolar Disorder, Alzheimer's Disease, Schizophrenia, and NeuroAIDS
9:00 am - 11:00 am

Prevalence, Nature and Clinical Significance of Neuropsychological Impairment Associated with HIV Infection
Robert K. Heaton, Ph.D.
University of California at San Diego

Brain involvement and neuropsychological (NP) impairments are common sequelae of HIV infection. Comprehensive NP test results with 1068 HIV-infected adults and seronegative controls demonstrate increased rates of impairment at all stages of HIV disease, especially in the more advanced, medically symptomatic stages (CDC-B and CDC-C). The average pattern of impairment across eight NP ability domains is consistent with preferential involvements of frontal-subcortical neural systems, but in HIV+ individuals the observed patterns of NP deficits are extremely variable. Even mild to moderate NP impairments in HIV infected persons can have major clinical significance, in that they are associated with lower employment rates, decreased independence in instrumental activities of daily living, worse driving records, poorer medication adherence, greater difficulty performing standardized work samples and laboratory-based versions of other daily living tasks, and early mortality.

Cognitive Impairment in the Course of Alzheimer's Disease
Alfred W. Kaszniak, Ph.D.
University of Arizona

This presentation will provide an overview of the cognitive deficits seen in Alzheimer's disease (AD), throughout the course of this chronic, progressive degenerative brain disease. Early in the course of AD, the most sensitive indicators of cognitive impairment are standardized tests of memory (particularly delayed recall) for recently presented verbal or nonverbal information. This correlates with neuropathology in hippocampal and entorhinal cortices that appears early in the illness course.

Mild memory impairments, measurable with sensitive neuropsychological tests, have been documented in apparently well-functioning persons several years prior to their diagnosis of AD. Also relatively early in the course of AD, individuals tend to show decreased verbal fluency, best documented by an ability to produce words within a given semantic category (e.g., names of animals or items that can be found in a supermarket). With disease progression, difficulties in spatial orientation and visuospatial abilities (e.g., ability to accurately draw a clock face), facial recognition, and language comprehension all occur. These impairments appear to reflect increasing neurofibrillary tangle and neuritic plaque involvement of the parietal and temporal association cortices. In addition, increasing problems in focusing and shifting attention and in "executive functions," associated with frontal system neuropathology, are seen with disease progression. Apathy, difficulty in shifting behavioral set to accommodate new task demands, impaired abstract reasoning, difficulty in the correct sequencing of behavior, and poor awareness of cognitive deficits are all aspects of executive dysfunction, and are also correlated with the degree of behavioral disinhibition and agitation among AD patients.

UPDATE SESSION II
10:45 am – 12:15 pm

Relapse Detection and Prevention in Anxiety Disorders
Matig R. Mavissakalian, M.D.
Case Western Reserve University

Only recently have controlled maintenance/discontinuation studies begun to demonstrate the prophylactic effectiveness of maintenance treatment and to elucidate the true risk of relapse following treatment discontinuation. This update will review the evidence for anxiety disorders, with particular emphasis on the treatment of panic disorder with serotonergic antidepressants and will discuss the practical and research implications of the data. It will be suggested that the clinical recommendation of wholesale long-term maintenance can no longer be supported by the less than 50% probability of relapse within 3 to 12 months of treatment discontinuation and that research needs to better elucidate and delineate the utility of prediction or early detection of relapse to enable targeted maintenance treatment.

Increasing Psychotropic Drug Response Predictability in African Americans and other Minorities
L. DiAnne Bradford, Ph.D.
Morehouse School of Medicine

Over 40 *CYP2D6* allelic variants have been discovered thus far. The alleles may be classified on the basis of the level of metabolic activity for which they encode *CYP2D6* enzymes, into "functional", "non-functional" (no activity) and "reduced function" groups. The proportion of each of these allele classifications differs significantly across race/ethnicity, resulting in unique metabolic profiles. Alleles, which encode for reduced metabolic activity are found at much higher frequencies in people of Asian and African descent - accounting for the "right shift" observed in metabolic ratios (MR) compared with Caucasians. Critical issues need to be addressed: 1) what are the allelic variants, SNPs and other upstream regulatory mechanism unique to populations of black African and Asian origin which are responsible for the observed decrease in MR; 2) well controlled clinical research on pharmacokinetics profiles and clinical correlates related to genotype are critically needed, and 3) the rapid expansion of knowledge on underlying mechanisms must be paralleled by rapid development of high throughput technology in order for individual predictability in drug response be realized.

Central NPY antagonizes behavioral consequences of stress. This was initially indicated by microinjection studies with NPY-receptor ligands, suggesting NPY-Y1 receptors to mediate anti-stress effects of NPY. Behavioral anti-stress actions of NPY are noteworthy in that 1) their magnitude surpasses that of other endogenous compounds; 2) they are produced across a wide range of animal models, normally thought to reflect different aspects of emotionality. These findings suggest that NPY acts with a high potency on a common core mechanism of emotionality and behavioral stress responses. This hypothesis is supported by behavioral studies in genetically modified animals. Increased emotionality has been reported in mice with a homologous recombination knock-out of the preproNPY-gene. More detailed studies have been made possible by a transgenic rat system, in which NPY is selectively over expressed within the hippocampus. These subjects display no overt phenotype under baseline conditions and have a normal endocrine stress response, but lack behavioral responses to stress. These findings point to the potential of the NPY system for developing novel pharmacological treatments of stress-related disorders, including anxiety and depression. Recent data additionally point to a role of NPY in the regulation of alcohol intake, and alcohol dependence emerges as a novel potential indication for compounds targeting the NPY system.

MGluR2/3 Receptors: A Neuroanatomically Selective Target with Relevance for Pathological Stress and Anxiety

Gary D. Tollefson, M.D., Ph.D.
Eli Lilly and Company

Modulation of glutamate neuronal transmission is a relatively under-explored area within neuropsychopharmacology. Metabotropic glutamate (mGlu) receptors modulate excitatory synaptic transmission, especially in neuroanatomic regions associated with fear/anxiety e.g., hippocampus, amygdala, pre-frontal cortex.

LY 354740 is a rationally designed, conformationally constrained analog of glutamate. It is a highly selective agonist for the mGlu2 and mGlu3 receptors and is active centrally when administered by parenteral and oral routes in animals. In pre-clinical models of anxiety or stress this compound will normalize the stress response in the elevated plus maze (Schoepp et al., 2001), prevent immobilization stress-induced BDNF expression (Gewirtz et al., 2002), suppress expression of fear potentiated startle in rats (Tizzano et al., 2001), block the suppression of the HPA axis response in non-human primates to adrenergic challenge, etc. (Coplan et al., 2001).

In human clinical pharmacology studies employing doses used in humans (100 – 200 mg bid), LY354740 dosing leads to CSF levels which activate mGlu2/3 human receptors. Experience to date with this compound has included evidence of a therapeutic effect in a CO_2 induced model of panic disorder and in a human potentiated startle model. Results from a large, multinational, double-blinded five-week GAD trial versus lorazepam and placebo will be presented. In brief, 738 subjects were randomized across 36 investigative sites. Both LY354740 arms (100 mg bid and 200 mg bid) and lorazepam separated from placebo on the LOCF baseline to endpoint change on the HAM-A. LY354740 was effective for both psychic and somatic subscales on the HAM-A. Both doses of LY354740 had rates of discontinuation due to an adverse drug reaction comparable to that seen with placebo. Lorazepam (mean dose 4-5 mg per day) was significantly less well tolerated (8.2% discontinuation rate due to side effects versus 2-3% for LY354740).

Treatment Development Session 7 *(continued)*
Novel Target-Driven Strategies for the Treatment of Mood and Anxiety Disorders
11:15 am – 12:30 pm

The most common treatment associated adverse events with LY354740 were nausea and headache. During a blinded one-week discontinuation phase, neither dose of LY354740 was differentiated from placebo, whereas lorazepam was significantly different from either placebo or LY354740 on the HAM-A and CGI-S.

These data together suggest that an approach through selective targeting of glutamatergic release via the mGluR2/3 receptor represents a promising and novel approach to the reduction of stress/anxiety disorders.

Ampakines: A New Class of Glutamatergic Agents with Potential Antidepressant Properties
Mohammed Shahid, Ph.D.
Organon Laboratories, Ltd.

Major advances in the future therapy of depression will most likely require a shift away from traditional mechanisms directly targeting central monoamine (5HT, noradrenaline, dopamine) pathways. Modulation of glutamatergic synaptic activity is an alternative approach, towards novel antidepressant drug discovery, for which there is growing supportive preclinical evidence in the literature. One particular mechanism involves the facilitation of glutamate α-amino-3-hydroxy-5-methly-4-isoazoleproprionic acid (AMPA) receptor mediated neurotransmission. Evidence will be presented to illustrate that positive allosteric modulators of the AMPA receptor (Ampakines®) show antidepressant-like properties in a range of independent animal tests.

PANEL 6
Advances in Medication Adherence in Psychotic Disorders
2:30 pm – 4:00 pm

Adherence and Concordance in Bipolar Disorder: Preliminary Data
Gary S. Sachs, M.D.
Massachusetts General Hospital

Adherence with pharmacological treatment regimens is a challenge for every branch of medicine. For psychiatry in general and Bipolar disorder in specific the challenge is heightened, since psychiatric illness often requires chronic treatment and frequently impacts perception and judgment.

Although, in accordance with guidelines recommending prophylactic treatment for Bipolar disorder, practitioners generally recommend long-term treatment, empirical studies indicate patients seldom heed these recommendations. Johnson and colleagues found that the following a hospital discharge in which lithium was prescribed for outpatient treatment, half the patients had discontinued treatment in less than twelve weeks. Such findings are troubling not only in light of data indicating early relapse and heightened mortality following discontinuation (Suppes et al, Tondo et al, Angst), but also because there is often considerable discordance between the treatment regarded as most appropriate and that which the patient is willing to take.

PANEL 6 (continued)
Advances in Medication Adherence in Psychotic Disorders
2:30 pm – 4:00 pm

STEP-BD is a large study focused on the effectiveness of treatments for Bipolar disorder. Preliminary data will be presented on the influence of a psychosocial interventions on drop out rates for subject receiving randomized pharmacological interventions for Bipolar depression.
Additional data will be presented on the treating psychiatrist's rating of "concordance" between their treatment recommendations and the treatment plan actually accepted by the patient.

Improving Adherence to Medications
Dawn I. Velligan, Ph.D.
University of Texas Health Science Center, San Antonio

Poor adherence to antipsychotic medications results in symptom exacerbation and relapse for those with psychotic disorders. It has been widely assumed that the introduction of the novel or atypical antipsychotic medications with more favorable side effect profiles and a broader range of efficacy than traditional neuroleptics would lead to improved medication adherence. Unfortunately, many obstacles to adequate adherence remain including denial or lack of insight, confusion, forgetting and a failure to establish routines that promote adherence. Psychosocial treatments that target these different adherence problems are being investigated. Compliance Therapy uses motivational interviewing to increase an individual's awareness of the need for medication and their willingness to take medication. Research suggests that subjects who participate in Compliance Therapy have more favorable attitudes toward medication-taking than those who participate in control treatments. Positive attitudes toward medication are a strong predictor of adherence. Cognitive Adaptation Training (CAT) is a novel psychosocial treatment that uses environmental supports such as the strategic placement of calendars, reminder signs, alarms, and special pill containers in the home environment to cue the taking of medication and to increase the likelihood that medication will be taken as prescribed. Patients participating in CAT have been found to have lower levels of symptomatology and fewer rehospitalizations than subjects participating in control treatments. Pharmacologic interventions such as depot neuroleptics are also an option for improving adherence. However, the side effects of these older medications may be problematic. The development of long-acting forms of the novel antipsychotic medications should be enthusiastically pursued.

PANEL 7
Brain Imaging Markers of Pharmacological Treatment in Children, Adolescents, and Adults
2:30 pm – 5:30 pm

BRAIN IMAGING MARKERS OF PHARMACOLOGICAL TREATMENT IN CHILDREN, ADOLESCENTS, AND ADULTS Part I. DRUG DEVELOPMENT

The first part of this panel addresses the use of neuroimaging in various phases of drug development. Imaging can aid in the development of novel pharmacological treatments by providing a compelling means of characterizing the next generation of therapeutics. Drs. Schmidt and Cole will discuss imaging approaches now being applied during CNS drug development and issues that arise when these methods are included in clinical research for the pharmaceutical industry. Dr. Henry will present magnetic resonance spectroscopy data from a study of R-fluoxetine and racemic fluoxetine in healthy volunteers designed to provide insight into dosing and safety issues likely to be encountered in clinical trials. Dr. Mathis will discuss the rational design of fluorescent and positron-labeled agents to image amyloid burden in brain for potential diagnostic and therapeutic applications in Alzheimer's disease.

Imaging with Drug Companies: What Can We Expect?
Mark E. Schmidt, MD
Novartis Pharma AG

The last 30 years of CNS drug development have brought forth a number of compounds that are well tolerated and bring relief to many patients with significant illness. Pharmaceutical companies developing the next generation of therapeutics are looking to entirely new drug targets with completely unknown pharmacology. In vivo imaging can provide compelling means of early characterization of these new drugs. To make the most effective use of imaging, methods should be considered and incorporated early in drug development. This can drive the need for parallel development of radioligand candidates, validation of techniques in pre-clinical models, and 'lead selection' of different approaches. Innovation in imaging techniques can create intellectual property and the need to respect new claims. Introduction of new methods to clinical trials generates the need for robust methods, standardization, and verification. Use of imaging data for registering a drug requires a priori agreement on objectives and methods with health authorities.

Several points relevant to clinical researchers will be discussed by Drs. Mark Schmidt and Patricia Cole from Novartis Pharmaceuticals, including the potential sources of new imaging tools from the pharmaceutical industry, issues that are arising with their development, recent applications of imaging to drug development, and 'lessons learned' from such experiences. The goal of these presentations will be for investigators to have an appreciation for the approaches now being applied during CNS drug development and issues that can arise when these methods are included in clinical research for the pharmaceutical industry.

Development and Application of Amyloid Imaging Agents for PET
C.A. Mathis, Ph.D.
University of Pittsburgh

Studies of amyloid-β (Aβ) protein metabolism are providing some of the most promising pre-clinical drug candidates for the treatment of Alzheimer's disease (AD). Major therapeutic candidates aimed at alterations in Aβ metabolism include secretase inhibitors (enzyme inhibitors that prevent the production of Aβ) and immunotherapy (both active and passive immunization approaches). Putative preventative treatments such as statin therapy and non-steroidal anti-inflammatory therapy also fall into the category of anti-amyloid therapies as they likely modify the metabolism of Aβ in a manner that would decrease

PANEL 7
Brain Imaging Markers of Pharmacological Treatment in Children, Adolescents, and Adults (continued)
2:30 pm – 5:30 pm

Aβ deposition. A critical hurdle on the path to full evaluation of the efficacy of anti-amyloid therapies has been the inability to assess the effect of treatments on the primary target, i.e., brain amyloid deposits. While promising anti-amyloid therapies are being intensely pursued, there is currently no accepted tool to directly assess the success of these agents in delaying or reversing amyloid deposition in humans. Optimally, it would be most desirable to initiate these therapies at the earliest signs of cognitive decline, or even prior to cognitive decline in patients at high risk for AD. Patients at these very early or pre-clinical stages of AD will have few cognitive deficits. In order to assess the efficacy of these anti-amyloid agents and to determine whether clinical efficacy or lack of efficacy is due to the success or failure of these treatments at decreasing amyloid deposition, it will be necessary to assess and quantify amyloid load in living patients.

This talk will describe initial human studies aimed at validating the use of a radiolabeled ligand as a positron emission tomography (PET) amyloid imaging agent. This ligand is known as {N-methyl-[C-11]}2-(4'-methylamino-phenyl)-6-hydroxy-benzothiazole (or [C-11]6-OH-BTA-1). This compound was developed at the University of Pittsburgh, and the first human studies were performed through collaborative studies with investigators at Uppsala University in Sweden, where the compound was given the name "Pittsburgh Compound B" or simply PIB. Follow-up PET imaging studies with this compound in mild cognitive impairment (MCI) subjects, mild to mid-stage AD patients, and age-matched control subjects are currently underway at the University of Pittsburgh. Successful development of this imaging tool would greatly facilitate the assessment of potentially beneficial anti-amyloid therapies for AD. In addition, this technology could have important implications for pre-clinical detection that may be critical in optimizing the chances of success for any AD treatment.

^{19}-F MRS in Drug Development: R-Fluoxetine as a Prototype

Michael E. Henry, M.D.
McLean Hospital

This talk will focus on the use of ^{19}-F MRS in drug development. Background on the method and its use in measuring the concentration of fluorinated compounds in target organs will be presented. Subsequently, a comparison of the central and peripheral pharmacokinetics of R-fluoxetine and racemic fluoxetine in healthy volunteers will be presented. Although the brain levels achieved with R-fluoxetine exceeded those achieved with the racemate, an analysis of the drug and metabolite composition of the serum suggests that the amount of active species was significantly less for the R-fluoxetine groups. The adverse events profile suggests that a therapeutic dose could not be achieved without significant toxicity.

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Part II. CLINICAL STUDIES OF CHILDREN AND ADOLESCENTS

Part II of this panel addresses clinical studies in child and adolescent neuropsychiatric disorders. The three speakers are all utilizing neuroimaging approaches to assess the effects of established pharmacologic treatments in clinical studies designed to elucidate underlying biological mechanisms of therapeutic effects, predict treatment responsiveness, and assess long-term effects on the developing brain. Dr. Rosenberg will describe an integrated series of clinical studies using MR spectroscopy and anatomic imaging to identify biomarkers in pediatric obsessive-compulsive disorder and major depressive disorder. Dr. Pliszka will extend this discussion to include the use of event-related potentials and functional MRI to identify brain targets of stimulant action in attention deficit hyperactivity disorder. Dr. Sikich will discuss the use of MR imaging modalities in the assessment of antipsychotic treatment in youth with schizophrenia. This series of presentations will inform clinicians and scientists of a wide range of applications of neuroimaging technologies in relationship to psychopharmacology.

Identification of Neuroimaging Biomarkers in Pediatric OCD and Depression
David R. Rosenberg, M.D.
Wayne State University

The identification of relevant biomarkers in obsessive compulsive disorder (OCD) and major depression (MDD) is a major aim of research into the illness. A sensitive and specific biomarker could enhance our understanding of the pathophysiology of these disorders and could also help to more narrowly define the phenotypes to reduce heterogeneity in genetic studies as well as facilitate early detection and therapeutic intervention. An ideal biomarker for OCD and MDD would have high sensitivity and specificity for the

disorders in affected patients. We describe an integrated series of neuroimaging studies using anatomic MRI and MR spectroscopy in pediatric patients with OCD pre-post treatment, pediatric patients with depression pre-post treatment as compared to healthy pediatric controls. Region-specific alterations in the neuronal marker, N-acetyl-asparate, choline compounds and glutamate/glutamine may distinguish pediatric OCD vs pediatric MDD and healthy controls at baseline and post-treatment. Specific anatomic and neurochemical patterns may help predict treatment response (or lack, thereof) in pediatric OCD and MDD.

Can Neuroimaging Identify Mechanisms Of Stimulant Action In Attention Deficit Hyperactivity Disorder?

Steven R. Pliszka, M.D.
University of Texas Health Science Center at San Antonio

To identify brain targets of stimulant action in attention deficit hyperactivity disorder (ADHD), the Stop Signal and Stroop Tasks are used as probes of inhibitory control in conjunction with event related potentials (ERP) and functional magnetic resonance imaging (fMRI) to study children with ADHD. Baseline studies are conducted in a medication-free state for comparisons to healthy age-matched controls. Following a five week double blind placebo crossover trial of methylphenidate, children with ADHD repeat the ERP and fMRI studies on placebo and on an optimal dose of methylphenidate for the evaluation of medication effects. Baseline ERP differences between patients and controls suggest dysfunction involving the right frontal lobe and anterior cingulate in ADHD. The right frontal dysfunction appears to be related to the initiation of inhibitory processing, while the anterior cingulate dysfunction may relate to error-recognition. Further analysis of data will focus on whether methylphenidate increases brain activity in the right frontal lobe and anterior cingulate and whether such increases correlate with clinical response. Practical issues involved in the neuroimaging of children will also be discussed.

Using Neuroimaging to Assess the Effects of Antipsychotic Treatment in Youth with Schizophrenia

Linmarie Sikich, M.D
University of North Carolina, Chapel Hill

Evaluation of antipsychotic treatments is complicated by the episodic nature of psychotic symptoms, the reliance upon patient reports and the absence of biological markers. Magnetic resonance techniques allow one to safely examine the same individual multiple times to evaluate longitudinal effects of treatment. We describe studies using volumetric magnetic resonance imaging and proton magnetic resonance spectroscopy (MRS) in youth with schizophrenia. Traditional antipsychotics appear to increase caudate volume over a period of years, while treatment with atypical antipsychotics does not appear to result in increases. Further, treatment with clozapine seems to reverse caudate volume changes related to earlier typical antipsychotic use. Our own work in psychotic adolescents examining regional brain structures after 8-20 weeks of treatment with either haloperidol or an atypical antipsychotic

PANEL 7
Brain Imaging Markers of Pharmacological Treatment in Children, Adolescents, and Adults (continued0
2:30 pm – 5:30 pm

(risperidone or olanzapine) fails to demonstrate acute treatment specific, regional volumetric changes. However, the MRS scans of these same patients suggest differential effects of traditional and atypical antipsychotics on NAA concentrations in the frontal cortex, hippocampus, and basal ganglia. The relationship of changes in NAA with treatment response, positive symptoms, negative symptoms and executive function will be described in an exploratory way. Neuroimaging techniques may be useful in understanding the benefits and actions of different antipsychotic drugs. Volumetric studies may correlate with specific clinical features of the disorder or toxicities of various agents. Magnetic resonance spectroscopy may provide information about neuronal effects and effects on disease progression.

TREATMENT DEVELOPMENT SESSION 8
Thinking Outside the Box: Future Directions in the Treatment of ADHD, Mood, and Anxiety Disorders in Children
2:30 pm – 4:30 pm

Use of Psychotropic Drugs in Children: A Pre-clinical Perspective
Susan L. Andersen, Ph.D.
McLean Hospital

Disorders that affect children pose a difficult choice for clinicians who treat them as they weigh the short-term gains of acute symptom relief against unknown, long-term consequences. What is known about the enduring effects of psychopharmacological treatment is based primarily on adult populations or on studies of limited duration in children and adolescents. Pre-clinical data that are available on the long-term consequences of juvenile drug exposure raise concerns that decisions predicated on adult effects are of limited value. Two themes emerge from these data that may be instrumental for novel approaches to treatment: first, the long-term consequences of early treatment become evident after the onset of puberty, suggesting that longer (ie, years post-treatment) clinical trials are needed for assessment; and second, juvenile exposure typically produces enduring responses that are opposite to that of adult exposure under similar conditions. In adults, long-term changes to drug exposure are those of accommodation, whereas juvenile exposure may lead to assimilation that in turn could alter the developmental trajectory of the underlying pathophysiology of the disorder. New approaches to treatment should focus on altering the trajectory of psychiatric disorders, with early intervention aimed at these delayed effects.

Breakthroughs in Pharmacological and Psychological Treatments for ADHD
James Swanson, Ph.D.

For pharmacological treatment of ADHD, immediate-release (IR) forms of stimulant medications were used almost exclusively for decades because of greater efficacy than first generation extended-release (ER) formulations. But based on a simple breakthrough (discovery of acute tolerance), new drug delivery profiles that achieve equal efficacy were developed for second generation ER formulations, which now have almost replaced IR stimulants. Now, a breakthrough is needed to address side effects of the stimulants. Control of "rate of drug delivery" may offer a way to reduce side effects and thus provide

TREATMENT DEVELOPMENT SESSION 8
Thinking Outside the Box: Future Directions in the Treatment of ADHD, Mood, and Anxiety Disorders in Children (continued)
2:30 pm – 4:30 pm

the next breakthrough in pharmacological treatment. Similarly, for over half a century, behavior modification has been the primary psychological treatment, but generalization remains a serious problem. No breakthrough has yet emerged, but recently several small "attention training" studies have produced positive results. This emerging literature will be reviewed. The possibility of a breakthrough in psychological treatments of ADHD will be discussed.

New Directions in the Psychopharmacology of Pediatric Anxiety
Daniel S. Pine, M.D.
National Institute of Mental Health

The current presentation will discuss directions for research in pediatric psychopharmacology by integrating insights from recent observations in both clinical and basic science research on anxiety. Three recent clinical observations markedly influence perspectives on pediatric psychopharmacology of anxiety disorders. First, most pediatric anxiety disorders represent transient conditions, though a subset of children with anxiety will suffer from chronic disability. Second, selective serotonin reuptake inhibitors (SSRIs) have been shown to effectively treat pediatric anxiety. Third, cognitive behavioral therapy has been shown to effectively treat pediatric anxiety. Similarly, two recent basic science observations may also be relevant to perspectives on pediatric anxiety. First, new pharmacological and psychotherapeutic interventions are being developed among adult humans, based on studies of the neural circuitry underlying the threat response. These include combined use of pharmacological and cognitive manipulations to alter threat behaviors. Second, developmental plasticity in fear-related systems has been precisely delineated through studies of rearing manipulations and genetic manipulations. This applies specifically to the sertonin system, based on results in genetically altered mice. The relevance of these basic science observations for the next wave of pediatric psychopharmacology studies will be considered.

Future Directions in the Treatment of Pediatric Bipolar Disorder
Ellen Leibenluft, M.D.
National Institute of Mental Health

Pediatric bipolar disorder (BPD) is now the subject of increased research attention, and with this attention has come a recognition that children with BPD frequently suffer from a treatment-resistant form of the illness. This presentation will focus on 1) the relevance of new research strategies in adult refractory BPD to research in pediatric BPD; and 2) the implications of developmental differences in the presentation of BPD for intervention research. Current research on the treatment of adult BPD uses insights about the molecular effects of known mood stabilizers to suggest new targets for therapeutic intervention and novel ways to measure outcome. Research on agents that appear to have neurotrophic or neuroprotective properties, including lithium and the antiglutamatergic agent riluzole, are of particular interest to those concerned about the developmental impact of psychotropic medications. In considering how to approach the treatment of refractory pediatric BPD, an important question is whether it is appropriate to study agents with favorable side-effect profiles but limited efficacy data in adults (e.g. important to consider the treatment implications of developmental aspects of the illness. The frequent

TREATMENT DEVELOPMENT SESSION 8
Thinking Outside the Box: Future Directions in the Treatment of ADHD, Mood, and Anxiety Disorders in Children (continued)
2:30 pm – 4:30 pm

riluzole) vs. agents with more supporting data but unfavorable side-effect profiles (e.g. clozapine). In addition to questions about how best to apply advances in adult BPD to research on children, it is comorbidity of ADHD and/or anxiety disorders with pediatric BPD, for example, highlights the need to study the efficacy and safety of mood stabilizers combined with either stimulants or SRI's in this population. Finally, irritability is one of the most impairing symptoms of the illness in children, but the lack of specific and sensitive rating scales for use in psychopharmacologic research reflects the paucity of data regarding the treatment of this important symptom.

Panel 8
New Treatment Developments for Somatoform Disorders
4:15 pm – 5:45 pm

Cognitive Behavior Therapy for Somatization Disorder
Lesley A. Allen, Ph.D.
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School

Somatization disorder is a debilitating and costly condition. Patients diagnosed with somatization disorder have high rates of disability, overuse health care services, and often prove refractory to treatment. To date, no psychotherapeutic nor pharmacological intervention has been found to produce clinically meaningful improvements in these patients' physical discomfort. This study examined the efficacy of a 10-session individual cognitive behavioral treatment (CBT) for somatization disorder.

Eighty-two men and women meeting DSM-IV criteria for somatization disorder were randomly assigned to receive either CBT along with standard medical care augmented by a psychiatric consultation letter (ASMC) or ASMC alone. Assessments of physical discomfort and physical functioning were conducted at baseline, 3 months after baseline (i.e., posttreatment), and 6 months after posttreatment (i.e., follow-up).

Seventy-six (92.7% of each group) patients completed all three assessments. Patients receiving CBT reported significantly greater improvement in their physical discomfort and physical functioning than did those receiving ASMC. Improvements in physical discomfort and physical functioning were not accounted for by improvements in mood.

A Randomized, Controlled Intervention Trial of Cognitive-Behavior Therapy For Hypochondriasis
Arthur J. Barsky, III, M.D.
Brigham and Women's Hospital

We conducted a randomized, controlled intervention trial of cognitive-behavior therapy (CBT) for hypochondriasis. This scripted, six-session, individual treatment was compared with medical care-as-usual. The CBT protocol was designed specifically to target the cognitive and perceptual factors that amplify hypochondriacal patients' somatic symptoms, disease fears and disease convictions.

Panel 8
New Treatment Developments for Somatoform Disorders (continued)
4:15 pm – 5:45 pm

Patients from primary care practices and volunteers responding to public announcements who exceeded a cut-off score on a hypochondriasis self-report questionnaire participated. Research interviews were conducted at baseline and 6 and 12 months following treatment. An intent-to-treat analytic strategy was employed. General Linear Modeling was used and a series of covariance models (ANCOVA and MANCOVA) were employed.

102 individuals were randomized to CBT and 85 were randomized to care-as-usual. A broad pattern of statistically and clinically significant treatment effects was apparent at both 6 and 12-month follow-up. CBT patients had significantly lower levels of hypochondriacal symptoms, hypochondriacal beliefs and behaviors, and health-related anxiety. They also had significantly less impairment of social role functioning and intermediate activities of daily life and significantly better self-rated global health. These between group effects persisted after adjusting for baseline sociodemographic characteristics and for comorbid psychiatric disorder. A completer's analysis revealed an even more robust treatment effect.

CBT in the Treatment of Somatization in Primary Care
Javier I. Escobar, M.D.
UMDNJ-Robert Wood Johnson Medical School

Patients presenting with high levels of medically unexplained symptoms are a frequent, frustrating and costly reality in primary care. While these patients may have underlying psychopathologies, the somatic symptom assumes a dominating role and patients reject psychological labels and referral. Recognition and management of these patients at the primary care site is essential and development of treatments that can be adapted to the primary care environment may have significant practical value.

This presentation reports on a controlled NIMH–funded study of CBT on a large, multiethnic sample of patients visiting a primary care clinic in New Jersey. 120 patients have entered the study thus far. About one half of the patients were randomly assigned to a treatment group, and the other half to a "consultation letter" control group. The treatment group received 10 sessions of a manualized Cognitive Behavior Therapy, designed for patients with somatoform disorders. Blind raters assessed change in somatic, mood and anxiety symptoms at baseline and frequent intervals with several instrumental measures.

Interim analyses show a significant effect of CBT on somatic symptom severity and functional outcomes compared to the control group. This effect seems to be independent of any effect CBT may have on mood or anxiety symptoms.

Friday, May 30, 2003

Food and Drug Administration Symposium
9:00 am – 12:00 pm

Surrogate Markers: Regulatory and Scientific Issues
Russell Katz, M.D.
Food and Drug Administration

FDA regulations and guidance documents provide for the possible approval of new products based on evidence for an effect on a surrogate marker that is thought to represent or predict clinical benefit. This talk will explore the regulatory issues that need to be addressed in considering claims based on surrogate endpoints, including: (1) a definition of a surrogate marker, (2) an exploration of the various factors involved in deciding in a particular setting whether surrogate endpoints may or may not be acceptable, (3) an exploration of why surrogates often fail, (4) approaches to validation of surrogates.

FDA View of Cognitive Deficits in Schizophrenia as a Target for Drug Development
Thomas Laughren, M.D.
Food and Drug Administration

There has been interest in developing drugs for the treatment of cognitive deficits in schizophrenia. This talk will explore the regulatory issues that need to be addressed in considering this new claim, in particular, the question of pseudospecificity. Criteria will be proposed for establishing cognitive deficits as a distinct aspect of this illness with regard to drug development. In addition, a number of practical issues in implementing a development program for this clinical entity will be considered: (1) identifying a population to study; (2) trial design; (3) assessments; (4) selecting primary and secondary endpoints; and (5) analysis plan.

An Association Between Atypical Antipsychotic Drug Use and Cerebrovascular Adverse Events in Patients with Dementia
Tarek Hammad, M.D., Ph.D.
Food and Drug Administration

On many occasions, important adverse events are identified after drug approval; this may occur while studying the drug for a new indication. It is important to be open to the possibility that a new population being treated with a drug approved for a different patient population may have a different safety profile. An example of this scenario will be presented quantifying the association between an atypical antipsychotic and cerebrovascular adverse events in patients with dementia.

Lumping or Splitting in Drug Claims Case in Point: Mood and Physical Symptoms of Premenstrual Dysphoric Disorder
Karen Brugge, M.D.
Food and Drug Administration

Drug development for an indication for a cluster of symptoms of a given disorder is an area that is of increasing interest to industry, the academic community and others. Developing a drug for treating a given symptom or symptom cluster, rather than the disorder itself is one approach. An example of this approach is targeting the cognitive deficits of schizophrenia, rather than for the entire disorder. A drug that is already found to be effective for the disorder, may be developed for demonstrating efficacy for a given symptom or cluster of symptoms of that

disorder. An example of this latter approach would be seeking a claim for the "physical" or "mood" symptoms of Premenstrual Dysphoric disorder (PMDD) for a drug that is already effective for PMDD. The potential caveats to these approaches in drug development will be discussed with a primary focus on the regulatory issues in seeking such claims. Making efficacy claims for the "physical" and "mood" symptoms of Premenstrual Dysphoric disorder (PMDD) will be used as an example in presenting these caveats and regulatory issues.

Blood (Sweat and Tears): Concentration Data in Regulatory Review
Cara Alfaro, Pharm.D.
Food and Drug Administration

Blood/plasma concentration data is included in virtually all preclinical and clinical submissions for investigational new drugs. This presentation will focus on ways in which blood/plasma concentration data is used in the evaluation of the safety and efficacy of drugs in the regulatory review process. Specific examples to be discussed include pharmacokinetic data and interpretation in drug metabolism, drug-drug interactions and dose/concentration-response issues.

POSTER ABSTRACT TOPIC INDEX

All poster presentations are copied verbatim and appear in category listing per day as outlined below:

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Session I – 1

APOE-ε4 Gene Status in High Functioning Elderly: Differential Effects of Lorazepam on Memory

Nunzio Pomara, M.D. [1, 2], Lisa Willoughby, Ph.D. [2], Keith Wesnes, Ph.D. [4],
David J. Greenblatt, M.D. [3], John J. Sidtis, Ph.D. [1, 2]

[1] Department of Psychiatry, New York University School of Medicine
[2] Nathan S. Kline Institute for Psychiatric Research
[3] Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine
[4] Cognitive Drug Research, Reading RG30 3TH UK

Background: The APOE- ε4 allele is an established genetic risk factor in the development of late-onset Alzheimer's Disease, but the evidence for more subtle cognitive sequelae in healthy, non-demented individuals who carry the APOE- ε4 allele has been mixed. Tests of baseline cognitive performance may not be sensitive in detecting subtle CNS alterations in this population. Acute pharmacological challenges in which a temporary impairment is induced in non-demented subjects is a potential alternative strategy for the detection of deleterious effects of the APOE- ε4 allele on CNS function in cognitively intact elderly. We previously examined the relationship between the APOE- ε4 allele and sensitivity to benzodiazepine induced cognitive toxicity in the elderly and found that possession of the APOE- ε4 allele may increase susceptibility to drug-induced impairment.

Methods: In the present study, verbal learning (Buschke Selective Reminding Test) was assessed in 62 highly educated (>12 yrs), non-demented adults during a 5 hr period after oral administration of placebo, 0.5 mg of lorazepam, or 1.0 mg of lorazepam. Twenty-four subjects (mean age = 66.25 yrs) were carriers of an APOE-e4 E ε4 allele (ε4 positive), 38 (mean age = 66.21 yrs) were not (ε4 negative). All subjects participated in each drug condition in sessions 1 week apart.

Results: There was a time-related, dose-dependent effect of lorazepam with measures of long-term recall generally decreasing with higher doses of lorazepam up to 2.5 hrs, followed by a significant improvement at 5 hrs. Comparisons based on APOE-ε4 allele demonstrated an ε4 by dose by time interaction such that at 5 hrs, the ε4 negative group was showing significant improvement in long-term memory following maximum drug impairment, but the ε4 positive group demonstrated a persistent deficit.

Conclusion: These results suggest that in cognitively intact, healthy, elderly adults, the effect of the APOE-ε4 allele is not necessarily seen in baseline function or even after a benzodiazepine cognitive challenge. Rather, the earliest evidence of the effects of the APOE- ε4 allele may be in carrier's inability to recover from a cognitive challenge in a normal fashion. Studying both the response to, and the recovery from cognitive challenges may provide insights into the role of the APOE- ε4 allele in Alzheimer's Disease and other age-related cognitive problems.

Source of Funding: NIMH grant: MH05994

Session I – 2

Secretin *IV* Induces Gene Activation and fMRI Changes in the Amygdala; Potential Relationship to Behavioral Improvements Seen in Treating Autistic Children

J. Rusche [1], D. Yurgelun-Todd [2], M. Goulet [1], J. Tay [1], R. Boismenu [1], P. Rioux [1], W. Herlihy [1]

[1] Repligen Corporation, Waltham, MA
[2] Cognitive Neuroimaging Laboratory, McLean Hospital, Harvard Medical School, Belmont, MA

Analysis of a placebo-controlled study in 126 autistic children age 3-6 receiving 3 doses of secretin *iv* identified a subset of children that showed improvement in reciprocal social interactions. The Autism Diagnostic Observation Schedule (ADOS) and a parent based measure, Clinical Global Impression of Change, were both improved ($P < 0.01$ and $P = 0.05$, respectively).

The effect of *iv* secretin in rat brain was measured using protein expression of the transcription factor Fos as a marker of cell activation. Secretin induced an increase in Fos within the central amygdala and area postrema. Gene expression analysis by microarray indicated egr-1, a transcription factor linked to neural plasticity activities, was also elevated in the central amygdala.

A placebo-controlled, double blind study of 12 neurotypical adult male subjects tested the effect of *iv* secretin on amygdala response when presented with fearful, happy, or neutral faces. To test whether treatment was associated with distinct patterns of activation, the two conditions of face viewing (pre and post treatment) were subjected to a subtraction analyses in SPM99 and hypotheses regarding the activation of the left and right amygdala were tested using a region of interest (ROI) approach. Subtraction of the treatment from baseline activation during the fear condition yielded significant ($P = 0.001$) activation in the right but not left amygdala when comparing secretin to placebo treatment. These clinical and non-clinical findings provide a rationale for the behavioral effect of secretin in autistic children and should be tested by further study.

Source of Funding: This work was supported by Repligen Corporation.

Session I – 3

Treatment-Emergent Polycystic Ovarian Syndrome in Women with Bipolar Disorder: Interim Report of the STEP-BD Ancillary Study

Hadine Joffe, M.D., M.Sc. [1], Lee S. Cohen, M.D. [1], Trisha Suppes, M.D., Ph.D. [2], Stephen Wisnewski, Ph.D. [3], Ellen B. Dennehy, Ph.D. [2], Phyllis Somers, B.A. [1], Caragh Reilly, B.A. [1], Wren McLaughlin, B.A. [1], Janet E. Hall, M.D. [4], Gary Sachs, M.D. [1]

[1] Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School
[2] Department of Psychiatry, University of Texas Southwestern Medical Center
[3] Epidemiology Data Center, University of Pittsburgh
[4] Reproductive Endocrine Unit, Department of Internal Medicine, MGH, Harvard Medical School

Background: Polycystic ovarian syndrome (PCOS) is a chronic disorder of infrequent ovulation and hyperandrogenism occurring in 4–7% of premenopausal women. In women with epilepsy, PCOS has been reported to occur more commonly in women taking valproate than in those taking other anticonvulsants. Preliminary data in small study populations of women with bipolar disorder have inconsistent findings. Establishing whether valproate increases the risk of treatment-emergent PCOS in women with bipolar disorder will determine if valproate causes reproductive-health risks for women with bipolar disorder.

Method: STEP-BD women with bipolar disorder were evaluated for menstrual abnormalities and hyperandrogenism (hirsutism, acne, male-pattern balding, and elevated testosterone and dehydroepiandrosterone-sulfate serum levels). Eligible subjects were women ages 18–45 taking at least one established or putative mood-stabilizer medication (valproate, lithium, lamotrigine, gabapentin, carbamazepine, oxcarbazepine, topiramate) for at least 3 months, but not on hormonal medication. PCOS was defined as <10 menstrual periods in the past year and evidence of hyperandrogenism. During the recruitment phase, the STEP-BD Data Safety Monitoring Board (DSMB) reviewed the incidence of treatment-emergent PCOS in women using valproate and those taking non-valproate mood-stabilizers.

Results: Of 502 STEP-enrolled women with bipolar disorder (age 18–45), 101 (20%) have enrolled and completed this study to date. The mean age was 34.4 (range 18–46) years, and the mean illness duration was 18.2 (range 1.1–39.8) years. Currently used medications included valproate (n=42), lithium (n=40), lamotrigine (n=35), topiramate (n=16), gabapentin (n=15), carbamazepine (n=8), and oxcarbazepine (n=5). After reviewing the progress of the trial, the DSMB recommended that enrollment continue. Based on initial sample size calculations of 218 valproate-users and 218 subjects not taking valproate, an interim analysis with a total of 42 valproate-users and 59 subjects not taking valproate did not provide sufficient power to stop the study prior to reaching the projected sample size.

Conclusions: A larger population of women with bipolar disorder is required to determine if the incidence of treatment-emergent PCOS with valproate exceeds the incidence of PCOS occurring with non-valproate mood-stabilizers. This STEP-BD ancillary study continues to enroll women to determine whether valproate is associated specifically with increased risk for PCOS in women with bipolar disorder.

Source of Funding: This study was supported by the following NIMH contracts: Massachusetts General Hospital #N01MH60011, University of Pittsburgh #N01MH60013, and University of Texas, San Antonio #N01MH60014.

Session I – 4

Serum Estrogen Levels in Perimenopause, Memory and Mood

Melinda L. Morgan, Ph.D. [1], Clay Van Batenburg, M.S.W. [1], Ian A.Cook, M.D. [1], Andrew Leuchter, M.D. [1], Andrea Rapkin, M.D. [1], Barbara Siegman, B.A. [1], Laura Mickes, B.A. [1]

[1] The Behavioral Pharmacology Laboratory, UCLA Neuropsychiatric Institute and the David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: During the onset of menopause, some women experience changes in memory and cognition, as well as depressive symptoms that may be severe enough to warrant antidepressant medication. Although some women respond fully to medication, others only respond partially with residual symptoms that negatively impact their quality of life. We investigated whether estrogen was beneficial to these women who experienced a partial response to antidepressant medications. Specifically, we examined the effects of estrogen on mood, memory and brain activity.

Methods: A 14-week double-blind placebo-controlled crossover design was used to study the effects of estrogen augmentation in depressed perimenopausal women (n= 11, enrollment is ongoing). Participants continued on the antidepressant prescribed by their primary physician throughout the study. Subjects were randomized to either conjugated estrogen (0.625 mg/d) or placebo. After the first treatment phase, a single blind two week wash out period was followed by the second treatment phase. Levels of follicle stimulating hormone (FSH) and estradiol were monitored throughout the study. Brain activity was measured with quantitative EEG cordance, a measure correlated with cerebral perfusion. The Buschke Selective Reminding Test evaluated verbal memory and the Hamilton Depression Scale assessed mood. Mood, memory, QEEG and hormone levels were assessed at baseline, at 6 weeks (end of phase 1) and 14 weeks (end of phase 2).

Results: After 6 weeks of estrogen, there was an increase in left temporal cordance; this was significantly correlated with an increase in serum estrogen ($p=.028$) Further, women with greater increases in estrogen performed better on the Bushke Selective Reminding Test ($p = .012$). Improved mood was also significantly predicted by estrogen and FSH ($p=.016$) No significant effects were found during the placebo phase.

Conclusion: In estrogen augmentation of women with perimenopausal depression, variation in serum levels of estrogen before and during treatment has significant effects on mood, memory and brain function. Future investigation of the efficacy of estrogen replacement should monitor serum estrogen levels.

Source of Funding: National Alliance for Research on Schizophrenia and Affective Disorders

Session I – 5

The Role of Anxiety and Hormonal Changes in Hot Flashes Among Perimenopausal Women

Ellen W. Freeman, Ph.D. [1, 2, 4], Mary D. Sammel, Sc.D. [3], Li Liu, M.D., M.S. [4]

[1] Departments of Obstetrics/Gynecology
[2] Department of Psychiatry
[3] Center for Clinical Epidemiology and Biostatistics
[4] Center for Research in Reproduction and Women's Health
University of Pennsylvania School of Medicine

Background: Hot flashes are the most common menopausal symptom. Although their association with estrogen withdrawal is established, a number of women are refractive to hormonal treatment, and there is little scientific information about other mood and behavioral factors that may play a role. This longitudinal study assessed the predictive effect of anxiety on hot flashes over a 4-year interval.

Methods: Population-based cohort of 436 women, ages 35 to 47 with regular menstrual cycles. At each of 6 assessment periods: anxiety was assessed using the Zung Anxiety Index; hot flashes (yes, no) and other variables were reported in structured interviews; depressive symptoms were assessed with the CES-D scale; BMI measures were obtained and subjects were assigned to menopausal categories based on menstrual cycle dates: Premenopausal (regular cycles 22-35 days); Early transition (within subject cycle length changes >= 7 days for at least 2 cycles); Late transition (3=11 months amenorrhea); post menopausal (>=12 month amenorrhea). Blood samples were collected between cycle days 2-6 in 2 consecutive cycles at each assessment to assay reproductive hormones. Repeated measurements were analyzed using generalized linear and logistic regression models.

Results: Anxiety was positively associated with hot flashes over the 4-year interval. Subjects scoring the highest tertial of anxiety were nearly 3 times more likely to report hot flashes than the low anxiety group (OR=2.66, CI=1.77, 3.99, P<0.0001). Baseline anxiety levels and changes in anxiety over the study interval remained significantly associated with hot flashes (P<0.001) after adjusting for time, race, age, menopausal status, depression, smoking and BMI. Variability of estradiol (not mean level) was significantly associated with hot flashes (P=0.05). Further analysis showed that anxiety levels were highest in the early transition to menopause (OR=1.50, CI=1.03, 2.19, P=0.04) and then decreased.

Conclusions: Anxiety is strongly associated with menopausal hot flashes. Baseline measures and changes in anxiety over the study interval remained highly significant after adjusting for depression and other factors. This association warrants further study and possible clinical investigation of treatments for anxiety to relieve distressing hot flashes.

Source of Funding: National Institute on Aging, Grant #AG 12745-07

Session I – 6

Brief Interpersonal Psychotherapy for Depression in Women: A Pilot Study

Holly A. Swartz, M.D., Ellen Frank, Ph.D., M. Katherine Shear, M.D.,
Michael E. Thase, M.D., John Scott, A.M.

University of Pittsburgh School of Medicine, Pittsburgh, PA

Objective: Interpersonal Psychotherapy (IPT) and pharmacotherapy are both efficacious treatments for depression; however, *post hoc* analyses suggest that reductions in depressive symptoms occur more quickly with pharmacotherapy than psychotherapy. This may be, in part, a result of IPT therapist and patient expectations that depression will improve in 12-16 weeks (the "standard" time-frame for IPT).

Brief IPT (IPT-B), a modified form of IPT, is an 8-session psychotherapy for depression. Patients are encouraged to make rapid interpersonal changes in this time period. In our pilot study of this intervention, a matched-case control design was used to evaluate 8-week outcomes following treatment with IPT-B (n=16) or sertraline (n=16).

Methods: Adult females meeting DSM-IV criteria for major depression and scoring > 15 on the Hamilton Rating Scale for Depression (HRSD-17) were treated openly with IPT-B. IPT-B treated subjects were matched on age, gender, and baseline depression severity to a sample of subjects treated with sertraline (134.38 ± 35.21mg). Independent raters assessed subjects serially from baseline through week 8. Linear mixed-effects regressions compared the 2 groups over 8 weeks of treatment.

Results: Significant time effects for HRSD-17 scores ($F=96.40$, $df=1,30$, $p<0.0001$) and GAS scores ($F=67.71$, $df=1,30$, $p<0.0001$) demonstrated that both groups improved over time. Significant time by group interaction effects indicate that the IPT-B group improved at a significantly greater rate than the SSRI group (HRSD-17 scores, $F=4.76$, $df=1,161$, $p=0.03$; GAS scores, $F=5.32$, $df=1,161$, $p=0.02$).

Conclusions: Preliminary findings suggest that IPT-B is at least as efficacious as sertraline as an 8-week treatment for major depressive disorder in women. The brevity of IPT-B motivates therapists and patients to work quickly, affording rapid relief from symptoms. IPT-B warrants further investigation as a brief treatment for depression in women.

Source of Funding: National Institute of Mental Health P30 MH-30915, K23 MH-64518, R01 MH-49115, R01 MH-41884

Session I – 7

Burden of Sexual Dysfunction with Antidepressant Treatments

Anita Clayton, M.D., Elizabeth McGarvey, Ed.D., Adrienne Keller, Ph.D., Relana Pinkerton, Ph.D.

University of Virginia Health System, Charlottesville, VA

Objective: The prevalence of global sexual dysfunction among patients treated with antidepressants ranges from 22% to 43% depending on specific medication. This study examines sexual dysfunction among patients who do not exhibit global dysfunction.

Methods: 6,297 adult outpatients (72% women) receiving antidepressant monotherapy were consecutively recruited from 1,101 primary care clinics. Global and subscale sexual dysfunction scores were obtained using the Changes in Sexual Functioning Questionnaire (CSFQ). The five subscales of the CSFQ assess sexual dysfunction in three phases of the sexual response cycle (desire, arousal, orgasm), and sexual pleasure.

Results: Among the 3,916 patients who did not meet CSFQ criteria for global sexual dysfunction, defined as total CSFQ score below threshold, 94.8% of women and 96.9% of men exhibited impairment on at least one subscale. Males were more likely than females to experience dysfunction in the desire phase (89% vs. 77%; χ^2=72.9, df=1, p<.001), and orgasmic dysfunction (83% vs. 43%; χ^2=514.9, df=1, p<.001), while females were more likely to experience dysfunction in the arousal phase (82% vs. 70%; χ^2=64.3, df=1, p<.001). Fluoxetine was the medication most likely to be associated with sexual dysfunction in all three phases of the response cycle (χ^2=23.9-43.7, df=8, p<.001). Bupropion SR and IR were least likely to cause sexual dysfunction with no sub-threshold scores on any subscale at 9% and 15% respectively.

Conclusions: Among patients who do not experience clinically significant global sexual dysfunction on antidepressant monotherapy, dysfunction in at least one phase of the sexual response cycle and/or sexual pleasure may reduce sexual health-related quality of life.

Source of Funding: GlaxoSmithKline

Session I – 8

Double-Blind Study Assessing Gender Based Variability in Response to Selective Serotonin Reuptake Inhibitors (SSRI) Treatment of Post Traumatic Stress Disorder (PTSD)

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Background: PTSD is a chronic and disabling psychiatric illness affecting 8-12% of the U.S. population[1, 2]. Studies have documented efficacy of various psychopharmacological agents, including SSRI's, in treating PTSD. Gender based differences in SSRI treatment of depression have been reported[5], but have not been formally addressed in PTSD[3, 4].

Method: 38 subjects aged 18-65 meeting DSM-IV criteria for PTSD with baseline Clinically Administered PTSD Scale (CAPS-I) score of more than 50 were enrolled. Patients taking other psychotropic medication or with substance abuse, serious medical illness, psychotic symptoms and any other primary AXIS I diagnosis detected by Structured Clinical Interview for DSM-IV with psychotic screen (SCID-P) were excluded. Subjects were randomly assigned in double blind manner to Citalopram (n=20), 20-50mgs/day, or Sertraline (n=18), 50-200mgs/day. Baseline and endpoint CAPS; Beck Depression Inventory (BDI); Impact of Event Scale (IES) and Clinical Global Impressions (CGI) scores were collected. Data was analyzed using T-tests with equal variance to compare differences between baselines and end scores for female and male groups.

Results: At the end of 10 weeks there was no statistically significant difference between pooled males (N=13) and females (N=25) in response to SSRI treatment of PTSD based on gender, as measured by differences in baseline and endpoint CAPS-I ($p=0.13$), IES ($p=0.72$), BDI ($p=0.57$), and CGI ($p=0.35$) scores. When analyzed separately both Sertraline (M=6, F=12) and Citalopram (M=7, F=13) showed no within the group differences ($p>0.07$) based on gender. Both groups improved significantly compared to baseline.

Conclusion: Results of this study did not show gender based differences in PTSD treatment response to SSRI's. Further studies on larger sample size are required.

Source of Funding: Forest Pharmaceuticals

Session I – 9

Efficacy of Sertraline in Improving Disability and Quality of Life Impairment in Severe Social Anxiety Disorder

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Objective: The goal of this investigation was to evaluate the effect of sertraline on QoL and work productivity in social anxiety disorder (SAD).

Methods: 415 outpatients with DSM-IV SAD (41% female, mean ± sd age, 35.1 ± 10.6 yrs) were randomized to 12 weeks of double-blind treatment with flexible doses (50-200 mg) of sertraline or placebo. QoL and functional assessments included the Quality of Life, Enjoyment, and Satisfaction scale (Q-LES-Q), the Sheehan disability inventory (SDI), and the Endicott work productivity score (EWP).

Results: Sertraline treated patients had a baseline LSAS of 91.3 ± 15.9 with a mean illness duration of 21 years and placebo patients had LSAS of 93.9 ± 16.0 with mean illness duration of 21.5 years. Treatment with sertraline resulted in significant improvement vs. placebo in the Q-LES-Q ($p < 0.001$), and in all 3 SDI factor scores. There was trend significant improvement on the EWP ($p = 0.10$). At baseline, 33% of patients had normative scores on the Q-LES-Q. At week 12, 59% on sertraline and 47% on placebo had achieved normative scores ($p=0.037$). Among patients with severe baseline impairment (> 1 sd below community mean, n=208) 46% on sertraline had normalized their QoL score by week 12, compared to 29% on placebo ($p=0.016$). In this subgroup, 48% receiving sertraline met CGI-I responder criteria compared to 32% who received placebo ($p=.02$)

Conclusion: Sertraline treatment of severe SAD was associated with significant improvement in quality of life and functioning, especially among the subgroup of patients with severe baseline impairment. Among responders in this subgroup, sertraline treatment resulted in significantly greater QoL improvement than with placebo treatment.

Source of Funding: Pfizer, Inc.

Session I – 10

Placebo Response and Social Anxiety Disorder: What Happened to "Reliable Predictors?"

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Background: The "placebo response problem" now plagues researchers in nearly every therapeutic area. The high frequency of failed anxiety [i.e. Panic Disorder and Generalized Anxiety Disorder] trials is well known; however, the comparatively low frequency of failed Social Anxiety Disorder [SAD] studies is perplexing. Are there key differences in SAD patients that contribute to the lower probability of having a "failed study"?

Methods: We analyzed data from more than 50 SAD patients randomly assigned to placebo treatment under double-blind conditions. Less than 25% of these patients responded to placebo as defined by final Clinical Global Impression [CGI] scores of 1 (very much improved) or 2 (much improved). We evaluated several variables previously reported as "predictors of placebo response," including Marital Status, Duration of Illness, Gender, Education and Severity of Illness.

Results: Our analyses did not corroborate the findings that Duration of Illness and Marital Status are predictive of placebo response; Severity of Illness also failed to demonstrate any predictive utility. Education appears to be a key variable in a number of ways, i.e. higher education correlated with a lesser degree of impairment at baseline ($p<.05$) and it was also associated with a lower Liebowitz Social Anxiety Scale [LSAS] score at endpoint ($p<.05$). Our analysis of gender indicated that females in SAD trials have a higher degree of impairment at baseline compared to males ($p<.01$); moreover, while they are no more or less responsive to placebo, the pre-existing differences in their LSAS scores indicate a lower probability of becoming categorized as placebo responders ($p<.05$), when defined by LSAS total score.

Conclusions: The fact that placebo response rates in SAD trials are lower than those in studies of other anxiety disorders is an important finding. The conventional wisdom about "reliable predictors" of placebo response seems dubious in light of these data. These findings raise methodological issues pertaining to optimal inclusion/exclusion criteria as well as caveats and precautions pertaining to the most appropriate methods of statistical analysis and data interpretation.

Source of Funding: Funding for this retrospective study was provided [internally] by Pharmacology Research Institute.

Session I – 11

Characteristics of Placebo Responders and Remitters in Pediatric ADHD Clinical Trials

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Background: Understanding the placebo response is a necessary prerequisite to improving clinical trial methodology. At a recent child and adolescent psychiatry research forum, a lack of data on the placebo response in children and adolescents was recognized. As part of the development of atomoxetine for the treatment of ADHD, Eli Lilly & Company has accumulated substantial data from placebo-controlled clinical trials involving children and adolescents with ADHD who are representative of patients seen in clinical settings. These data were analyzed to identify demographic characteristics of children and adolescents that might predict placebo response in clinical trials.

Method: Data were collapsed across 347 patients who participated in one of five randomized, placebo-controlled trials. Responders were defined as those with a reduction of at least 10 in the ADHD-RS Total T-score. Remitters were defined as those with an ADHD-RS total T-score of 65 or less. Demographic variables such as age, origin, gender, ADHD subtype, ADHD severity, comorbid ODD, and prior stimulant use were examined.

Results: Baseline characteristics across studies were similar. ADHD subtype and prior stimulant exposure were significant predictors of placebo response ($p=.016$ and $p=.035$, respectively). Patients with inattentive subtype as well as those who were stimulant-naïve were more likely to be classified as placebo responders. Results are similar for predictors of remission. Additionally, the average baseline severity was 7.2 points lower in those classified as remitters ($p<.001$). Among remitters, there was a lower percentage of patients with ODD ($p=.020$).

Conclusion: Inclusion/exclusion criteria based on ADHD subtype and/or prior stimulant treatment may affect the placebo response in pediatric ADHD clinical trials. Criteria that work to decrease the placebo response rate may conversely make study samples less representative of the population being treated.

Source of Funding: Research supported by Eli Lilly & Company

Session I – 12

Minimizing Placebo Response and Variability in a GAD Trial

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Background: The problem of high placebo response in short-term, double-blind trials in anxiety and depression has been well-described. High placebo response rates increase the likelihood of a failed trial when subjective rating instruments such as the HAM-A are used to assess efficacy. In an attempt to maximize the likelihood of determining the efficacy of an investigational anxiolytic compound in patients with Generalized Anxiety Disorder (GAD), several techniques aimed at either reducing the placebo response and/or reducing the measurement variability of the primary efficacy parameter were employed.

Methods: This was a randomized, double-blind, placebo- and alprazolam controlled study of the efficacy and safety of 2 dose levels of an investigational anxiolytic agent in patients with GAD. A proven anxiolytic (alprazolam) treatment group was included as a means of verifying the sensitivity of the study methodology. Approximately 280 patients were to be randomized evenly across 4 treatment groups including placebo, alprazolam, test agent (TA) low dose, or TA high dose. Treatment was carried out over 8 weeks and included a one-week, single-blind placebo run-in, 6 weeks of double-blind therapy, and one week single-blind washout. The primary measure of efficacy was the HAM-A. Secondary variables included the CGI-S and CGI-I. Efficacy was assessed at screening, baseline, end of double-blind treatment weeks 1, 2, 4 and 6 and following the washout. Primary analysis was the mean change from baseline in the HAM-A scores. Secondary analyses included a calculation of percent responders on the HAM-A (50% reduction in score from baseline) and the CGI-I (rating of 1 very much improved or, 2 much improved). Techniques utilized in an attempt to control placebo response and rating variability included: 1) intensive rater consensus development and recalibration sessions for the HAM-A, 2) patient and rater education of expectations in clinical trials (presentation and video), 3) a requirement that the minimum severity of anxiety required at baseline for randomization be determined on a scale other than that used for the primary analysis (CGI-S of 4 or higher), 4) single-blind run-in, and 5) minimal patient contact by minimizing the number of visits and assessments performed.

Results: Baseline HAM-A scores and week 6 LOCF mean change from baseline are summarized below:

Treatment Group	N	Mean Baseline (SD)	Mean Change at week 6 LOCF (SE)	Mean Difference from Placebo
TA low	72	23.46 (3.09)	-6.45 (0.75)	0.78 (NS)
TA high	71	23.28 (3.38)	-8.43 (0.75)	-1.20 (NS)
Alprazolam	77	23.36 (3.1)	-9.59 (0.72)	-2.36 (p=0.019)
placebo	72	23.51 (3.68)	-7.23 (0.74)	-

Variability on the HAM-A ratings was relatively low at LOCF. Pooled standard deviation was approximately 6.1 as compared to an historical estimate of 8.0. HAM-A and CGI-I response rates are summarized below:

Treatment Group	HAM-A Responders (%)	CGI-I Responders (%)
TA low	22.2 (NS vs. pbo)	21.4 (NS vs. pbo)
TA high	32.4 (NS vs. pbo)	43.5 (NS vs. pbo)
Alprazolam	44.2 (p=0.02 vs. pbo)	54.7 (p<0.01 vs. pbo)
placebo	25.0	29.6

The placebo response rate was low as demonstrated by the HAM-A and CGI-I responder analyses.

Conclusions: Results of the trial were clear and easily interpretable. The trial is considered positive as evidenced by the differentiation of the active control from placebo. The methods employed resulted in low placebo response rate and rating variability, thereby allowing for accurate, sensitive assessment and decision making regarding the test agent.

Source of Funding: Pfizer, Inc.

Session I – 13

The High Frequency of In-Study New Rater Qualification

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Background: Ideally, all raters in CNS clinical studies are qualified via inter-rater reliability programs that minimize variance between raters and maximize ratings accuracy. Qualification of raters is generally conducted at investigator meetings. Many potential raters do not attend the investigator meeting or are added once the study begins. Consequently, new raters must be qualified in-study. The impact of new raters qualified in-study on study quality and outcome is not known. In this survey, we have identified the magnitude of new raters qualified in-study and considered some of the parameters that affect this issue.

Methods: Rater qualification program conducted by Pharmastar LLC since 2001 involving at least 50 raters, 6 months of enrollment, and at least 15 clinical trial sites were selected for analysis in this survey. Studies included mood and anxiety disorders, schizophrenia, and several variants of dementia. Data examined included the therapeutic area and ratings instruments used, number of raters, sites, countries, languages, and study specifics (length of enrollment, length of study). Frequency analysis was performed for new rater qualification by therapeutic area.

Results: 16 studies met the above analysis criteria for this survey including 5 mood disorder, 4 schizophrenia, and 7 dementia studies. The range of in-study new rater qualification varied from 10-54% between studies. Dementia studies revealed the highest frequencies for new raters. Length of enrollment and length of study were the two most important contributing variables. When controlled for length of enrollment and study, the use of multiple countries and/or languages did not affect the frequency of new rater qualification.

Conclusion: We found high frequencies of in-study new rater qualification. Further analysis of rater change by individual patient and identification of additional versus replacement raters by site is needed. Some mitigating steps that reduce the higher new rater frequencies include more careful trial site identification, specific pre-qualification programs conducted prior to the investigator meeting, and more invitees to the investigator meeting. These interventions improve inter-rater reliability and may positively affect study outcome as well.

Source of Funding: Data from this survey comes from vendor contracts provided by: Novartis, Janssen Pharmaceutica, Otsuka, Sanofi-Synthelabo, Solvay, Eisai, GSK, Forest Laboratories.

Session I – 14

Rating the Raters: An Evaluation of Audiotaped Hamilton Depression Rating Scale (HAMD) Interviews

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Background: Signal detection is potentially influenced by behaviors of raters at investigative sites participating in industry-sponsored clinical trials of antidepressants.

Methods: 790 outpatients in two similar placebo-controlled studies of antidepressants conducted at 32 sites were asked if their baseline HAMD interviews could be audiotaped. A sample of the 712 tapes made was blindly reviewed by a single experienced HAMD rater (DS) who evaluated rater behaviors using the Rater Applied Performance Scale (Lipsitz et al., unpublished): adherence to the SIGH-D (Williams, 1988), follow-up, clarification, neutrality, rapport, and adequacy of information obtained. DS also measured interview length, evaluated patient verbal skills and scored 15 HAMD items for each tape (Retardation and Agitation HAMD items not scored). 77 tapes from 13 sites were evaluated sufficiently to be included in statistical analyses. After all tapes were evaluated, sponsors disclosed baseline and endpoint HAMD scores for the patients on the tapes (judged by original raters), whether each of them received an active drug (D, N=42) or placebo (P, N=35), and mean HAMD changes observed in all D and P patients at each site.

Results: Correlation between DS's 15-item total and original rater's 17-item total HAMD score was good (r=0.692). Interviews tended to be brief (mean 13, range 3-35 minutes). Adherence (68% of tapes), follow-up (77%), and adequacy (58%) were rated Unsatisfactory or Fair. Clarification, neutrality, rapport, and patient verbal skill were most frequently rated Fair or Good. For all 77 patients in our sample, mean (±SEM) HAMD changes were D=12.4 (±1.17) and P=10.3 (±1.14); this difference was not statistically significant (p=0.197). When only 30 patients with clarification rated Good or Excellent at baseline were considered, mean HAMD changes were D=14.9 (±1.79) and P=8.9 (±1.46); this treatment difference was statistically significant (p=0.014). Adherence and interview length also showed promise for improving separation. Sites with longer mean taped interview length were those with larger differences between D and P (p=0.008).

Conclusions: HAMD interviews are often brief and cursory. Recognizing and improving rater behaviors, such as clarification of patient responses, may allow increased drug-placebo separation.

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Session I – 15

Training Raters to Assess Adult ADHD: Reliability of Ratings

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Background: Attention Deficit Hyperactivity Disorder (ADHD) is a common and impairing neuro-psychiatric condition, affecting both children and adults. The standardization of ADHD ratings in adults is important given their differing symptom presentation. We report the results of rater standardization in a large scale trial of the norepinephrine re-uptake inhibitor, atomoxetine in adults with ADHD.

Methods: Training of 91 raters occurred prior to initiation of a 536 patient, 31 site trial of atomoxetine. Scales involved in the trial were Conners Diagnostic Scale and the Conners Adult ADHD Scale: Investigator (CAARS: Inv). The training was for the pivotal outcome item in the trial, the investigator administered Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS), which was extracted from 18 items of the CAARS: Inv. Training procedures included a preparation session, including an overview of the condition, review of scales - including prompts and patient examples for each item, and small group observation of an expert live interview. Formal rater standardization of CAARS: investigator ratings was via scoring a live interview of adult with ADHD. Internal consistency of symptom scores was assessed by Cronbach's alpha. Agreement among raters on total scores was established in two ways: 1) Kappa coefficient: rater agreement for each item, with the per cent of raters that had identical item by item scores; and 2) Intra-class correlation coefficients: reliability.

Results: Statistical comparisons for ADHD-RS total scores are shown below:

Mean $\pm$ SD	$10^{th}/90^{th}$ %ile	Cronbach's Alpha	Per cent Agreement	Kappa	Intraclass Correlation	Reliability
31.0 $\pm$ 3.5	27/36	.78	65	.50	0.75	.87

Conclusions: 1) The ADHD-RS is a highly reliable instrument for assessment of adult ADHD. 2) The reliability of ADHD-RS total scores was substantial as measured by Cronbach's alpha and intraclass correlation coefficient. 65% of the time rater's scored fully identical matches on the entire scale, which was moderate as measured by the kappa coefficient. 3) It is not surprising that intraclass correlations were higher than these kappa coefficients as the latter require rater's to record identical scores, whereas intraclass correlations do not. Analyses of subset scores and individual ADHD-RS items will be discussed at the time of presentation.

Source of Funding: Research Grant from Eli Lilly and Company.

Session I – 16

A Scale for Rating the Applied Performance of Clinical Raters in Multi-Site Trials: Development and Reliability

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Background: Previous attempts to measure rater competence and interrater reliability among clinical raters have utilized passive measures such as ratings from videotaped interviews. However, little is known about how well raters conduct assessments on real patients and how reliably they apply scoring criteria in actual assessment situations. In multi-site trials, there is growing recognition of the need for monitoring and review of actual assessment sessions and many studies now include ongoing monitoring procedures to improve quality control. However, there is no systematic measure to quantify raters' applied performance.

Methods: We developed the Rater Applied Performance Scale (RAPS) to measures six dimensions of rater performance: 1) Adherence, 2) Follow-up, 3) Clarification, 4) Neutrality, 5) Rapport, and 6) Accuracy of Scoring. RAPS ratings are based on audiotape reviews of actual assessment interviews with study patients. To assess the reliability of the RAPS, three reviewers independently rated N=15 audiotaped Hamilton Depression Scale interviews collected from a multi-site depression trial. Internal consistency was assessed using coefficient alpha. Interrater (i.e., inter-reviewer) reliability was assessed using intraclass correlation coefficients (ICCs) for total scale score and individual item ratings.

Results: Internal consistency of the six item RAPS scale was high in this sample of reviews. Alpha coefficients was .92 overall and inter-correlations among individual items ranged from moderate to high (r=.53 – r=.82). Interrater (i.e., inter-reviewer) reliability for the total scale score was excellent Intraclass correlation coefficient for the total RAPS scores was also excellent (ICC=.89). Interrater reliability for Individual RAPS items ranged from good (.69 for neutrality) to excellent (.87 for adherence).

Conclusions: Now that multi-site trials studies are paying more attention to how raters ascertain the clinical ratings that may determine a trial's success of failure, a systematic approach to measuring rater performance is needed. A quantitative measure will be essential for qualifying raters to participate in trials, for monitoring adequacy of ongoing ratings among a large population of raters, and for profiling the relative performance of raters and sites for future selection and exclusion. Preliminary data on the RAPS show that individual items on this scale form a coherent dimensional rating of rater performance. Three independent reviewers agreed closely on RAPS ratings in this sample, suggesting that reviewer ratings are not idiosyncratic and that multiple reviewers can generate meaningful ratings for later analysis of rater performance.

Source of Funding: This work was supported in part by NIMH Grant #K08-MH01575 to Dr. Lipsitz.

Session I – 17

Compiled Mood and Anxiety Rating Scales (C-MARS): MADRS, SIGH-SAD, IDS-C, YMRS, and HAM-A Compiled

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Background: Multiple assessments are needed to cover the range of affective disorders symptoms and to allow cross trial comparisons. Using several tools makes the process inefficient and may result in contradictory patient responses and inadequate clinician probing.

Significance: The objective of this study was to improve rating efficiency, and precision of inquiry without compromising reliability when multiple tools are used.

Methods: MADRS, SIGH-SAD, IDS-C, YMRS, and HAM-A have 10, 29, 30, 11, 14, items with corresponding administration time of 15, 30-45, 30, 15-30, 15-30 minutes, respectively. We compiled them into C-MARS with 97 items that can be used flexibly to obtain separate scores for MADRS; SIGH-SAD, HAM-D 17, 21, 24, 8 bipolar depression items; IDS-C; HAM-A; and YMRS. Categories of assessment included mood, its variation and quality, thought content, suicide, sleep, appetite, cognitive and psychomotor functioning, energy, hedonic tone, somatic symptoms, insight, psychotic symptoms, and observations.

Four experienced clinicians assessed sixteen subjects (16) with mood/anxiety disorders. Half the subjects were assessed with MADRS, SIGH-SAD, HAM-A, IDS, YMRS, then reassessed, same day, using C-MARS. Order of assessment was reversed for the other half. Clinicians had inter-rater reliability for all measures.

Results: The interclass correlations (ICC) were MADRS/ C-MARS-MADRS, .93; HAM-A/ C-MARS-HAM-A, .89;YMRS/ C-MARS-YMRS, .91;IDS-C/ C-MARS-IDS-C, .92; and SIGH-SAD/ C-MARS-SIGH-SAD, .91. The administration time with C-MARS varied from 40-90 minutes. Considering the minimum-maximum time guides for the administration of these measures which totals to 90-150 minutes (see above), C-MARS requires 50-60 minutes less in administration time than if these measures were administered separately.

Conclusion: CMARS is reliable, efficient, diminishes redundancy, errors, and inadequate probing that can occur with multiple assessments. It is comprehensive and permits cross-trial comparisons. It can be used flexibly to obtain scores for all or some of the measures of which it consists. In addition, clinicians and patients reported (anecdotal) a preference for C-MARS stating the above named factors.

Source of Funding: Government

Session I – 18

Development of a Standardized HAMD Inter-Rater Reliability Training Program for the Hamilton Depression Scale Using Internet-Based Technologies: Results from a Pilot Study

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Background: The issue of rater training and rater quality has been largely overlooked in the growing concern over failed trials**.** Poor inter-rater reliability contributes to error variance, which decreases power and increases the risk for failed trials. This is particularly problematic with the Hamilton Depression Scale (HAMD), due to lack of standardized training approaches and scoring conventions. The goal of this study was to develop a model for rater training designed specifically for multi-center clinical trials. Our goal was to develop an educational program that will help raters become highly competent in both their didactic knowledge and in their applied skills, as well as reliable with each other. The challenge was to provide this interactive training from a centralized location to diverse sites. The use of web-based technologies allows for such an approach.

Methods: The program consists of two components: a didactic component, (consisting of an interactive web tutorial), and an applied component, (consisting of live observation and feedback using videoconferencing). The web tutorial reviewed the HAMD item content and conventions, and general rules for scale administration. It utilized interactive testing and feedback throughout the tutorial for immediate reinforcement of learning, using audio, video, and text. For applied training, trainees interviewed a standardized patient who was at a remote location using videoconferencing, with the trainer observing and providing live feedback. Following training, inter-rater reliability was tested with the same methodology, i.e., trainees conducted independent interviews of the same (remote) patient at different times using videoconferencing.

Results: The program was pilot tested with 9 raters from a single site. Results found a significant increase in didactic knowledge pre-to-post testing, with the mean number of incorrect answers decreasing from 6.5 (SD=1.64) to 1.3 (SD=1.03), $t(5)=7.35$, $p=.001$ (20 item exam). Seventy-five percent of the trainees' interviews were within 2 points of the trainers score. Inter-rater reliability (intraclass correlation) (based on trainees actual interviews) was .97, $p<.0001$.

Conclusion: Results support the feasibility of this methodology for improving rater training. An NIMH funded study is currently underway examining this methodology in a multi-site trial.

Source of Funding: This study was supported by NIMH contract # N43MH12049 awarded to Kenneth A. Kobak, Ph.D., Research Training Associates.

Session I – 19

The GRID-HAMD: A Reliability Study in Patients with Major Depression

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[11] Johnson and Johnson

Introduction: The GRID-HAMD is a new standardized scoring system developed as a collaborative effort by academic, governmental, and pharmaceutical industry researchers. The GRID-HAMD operationalizes intensity and frequency of each item, and allows these to be rated simultaneously. Conventions for administering the scale, as well as a structured interview guide, have been developed and pilot tested for usability. To assess the reliability of the GRID-HAMD, clinical investigators taking part in an ongoing open-label multi-center depression study administered the GRID-HAMD to patients at baseline visit and at week 4.

Methods: All patients in this study met criteria for moderate to severe major depression (DSM-IV). Raters were trained on the use of the GRID-HAMD by a brief teleconference with developers of the GRID-HAMD. The GRID-HAMD was administered to consenting patients twice at the baseline visit by different raters, and twice at week 4 by the same two raters, whenever possible. At the interim visits and after the week-4 visit, patients were assessed with the Structured Interview Guide for the HAMD (Williams, 1988) by a single rater.

Results: Data from 45 patients assessed at baseline, week 4, or both were available. 20 raters across 5 investigative sites provided ratings. Data were combined across sites and rater pairs. Intra-class correlation coefficient (ICC) for the total 17-item score was 0.75 at baseline (n=34) and 0.82 at week 4 (n=31). Percent frequency at which raters entered identical item scores (i.e., utilized the same intensity and frequency determination) was calculated for all pairs of raters. Minimum percent agreement was 69.2; maximum was 95.1 for items presented in GRID format. Pearson's correlation for the total 17-item change score (baseline score minus week 4 score) of patients rated twice at baseline and twice at week 4 by the same rater pairs was 0.92 (n=20). Additional analyses will be possible when the study is completed.

Conclusions: The GRID-HAMD is reliable, with minimal training. Raters in this study used the GRID-HAMD consistently, indicating its clinical utility and value as a method of obtaining reliable depression severity ratings.

Source of Funding: Companies contributing to the Depression Rating Scale Standardization Team (DRSST)

Session I – 20

Pre-Randomization Changes in Hamilton Depression Rating Scale Scores are Predictive of Placebo Response and Drug-Placebo Separation

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Boehringer-Ingelheim

Background: Previously we described a novel trial design whereby depressive severity criteria, as measured by the Hamilton Depression Rating Scale (HDRS), was present at Screen but not at Baseline. We reported that patients who worsened between Screen and Baseline (worseners) had the highest placebo response and poorest drug-placebo separation. Patients showing no or minimal (1-point on HDRS) improvement had the lowest placebo response and the best drug-placebo separation, while patients with greater improvement had an intermediate level of placebo response and also had poor drug-placebo separation.

Goals: 1) To examine the time course of the placebo response for each of the three groups of patients; 2) To analyse the drug-placebo response of each group based on responder and remitter criteria; 3) To determine whether there were any differences in key demographic variables between the three groups of patients; 4) To determine whether having different raters between Screen and Baseline could account for the Screen-to-Baseline changes in HAMD score observed in the three groups

Methods: 4 double-blind studies were conducted using a design in which severity inclusion criteria were present at Screen but not Baseline.

Results: Worseners showed a very rapid placebo response and had the highest placebo response across all timepoints as compared to the other two groups of patients. Further, patients with no or modest change in HDRS score between Screen and Baseline exhibited the best drug-placebo separation, using remitter and responder criteria. There were no significant differences in any of the key demographic variables analysed, including gender, age, and mean duration of current episode. Moreover, there were no differences in the percentage of patients with different raters between Screen and Baseline across the three groups.

Conclusion: Pre-randomization worsening is predictive of rapid and heightened placebo response. Pre-randomization changes in HDRS score are also predictive of drug-placebo separation using responder and remitter criteria. None of the demographic variables examined were related to pre-randomization change in HDRS score. Further, the pre-randomization changes observed in the three groups is not due to having different raters between Screen and Baseline.

Source of Funding: Boehringer Ingelheim.

Session I – 21

Item Response Analyses of HAMD Data from Three Pharmaceutical Companies: A Useful Approach for Assessing and Refining Psychometric Instruments

Dr. Kenneth R. Evans [1], Dr Michael Gibertini [2], Dr Nina Engelhardt [3], Professor Per Bech [4], Dr. Amir Kalali [5], Dr. Ken Kobak [6], Dr. Josh Lipsitz [7], Dr. Jason Olin [8], Dr. Jay Pearson [9], Dr. Margaret Rothman [10], Dr. Janet Williams [11]

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[3] Eli Lilly, [4] Psychiatric Research Institute, Frederiksborg General Hospital, Denmark
[5] Quintiles Inc. and University of California Irvine
[6] Healthcare Technology Systems
[7] New York State Psychiatric Institute, Columbia University, and Research Training Associates
[8] National Institute of Mental Health, [9] Merck Research Laboratories
[10] Johnson & Johnson, [11] New York State Psychiatric Institute and Columbia University

Background: The utility of a number of Hamilton Depression Rating Scale (HAMD) items has been questioned. For an item on a clinical assessment tool to be "useful" it is necessary that differences in overall severity of the illness be reflected in the scores of the individual items; symptoms that are not sensitive to changes in severity are not useful in assessing response to treatment. This study examined the usefulness of the HAMD Loss of Weight, Insomnia and Insightitems by utilizing a nonparametric item response (IR) model.

Methods: Datasets comprising five separate outpatient antidepressant trials (sponsored by three pharmaceutical companies) were used to generate Option Characteristic Curves (OCCs) for the Insight, Insomnia and Weight Loss items of the HAMD. OCCs show the probability that a given score (i.e. 0, 1, 2 etc) will be assigned at each level of depressive severity. In addition, since the GRID-HAMD assesses both severity and frequency of symptoms, OCCs were generated for both of these dimensions for the Insomnia items.

Results: For the Loss of Weight and Insight items, the probability of a response option being endorsed did not change in relation to change in illness severity. Similar results were observed in studies from all three sponsors, and in both the GRID-HAMD and SIGH-D interview formats. The insomnia items have utility from an IR perspective, although the frequency of insomnia appeared to be of little relevance.

Conclusions: IR analyses reveal that the Loss of Weight and Insight items were consistently poor in the discrimination of depressive severity, irrespective of the method of scale administration, study design or sponsor. Results suggest that insomnia is relevant to depression, but that the distinction between 1-2 nights of insomnia and 3-5 nights of insomnia may not be important to the discrimination of depressive severity. Relatively minor modifications to the scoring conventions of the insomnia items could improve their psychometric properties. IR methods appear to be a valuable tool to assess positive and negative properties of clinical assessment tools.

Supported By: Boehringer-Ingelheim, Eli Lilly, Organon, Quintiles, Merck, Johnson and Johnson

Session I – 22

The Electronic Medical Record as a Point-of-Care Recruitment Tool for a Psychiatric Treatment Study in Primary Care Settings

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Background: Recruitment of subjects is a common barrier to completing clinical trials. This problem is compounded for psychiatric studies in busy primary care settings, where the pace and culture of medical practice often disincline practitioners from referring their patients. The objective of this study was to pilot use of the electronic medical record as tool for recruiting subjects to participate in a study of patients treated with antidepressants by primary care physicians.

Methods: The study site was a large academic primary care medicine practice serving approximately 80,000 patients. An online medical record has been in use in this practice for over a decade. Every exam room includes a networked computer terminal. We added an automatic query to the system which was programmed to identify potential subjects for a study of antidepressant treatment outcomes.

Results: The program successfully identified potential subjects who met the recruitment criteria 100% of the time. Primary care physicians were reminded about the study at an appropriate point within the flow of patient care. Whenever an antidepressant prescription was written in OMR for a patient who had not been prescribed an antidepressant for at least three months, a reminder about the study appeared on the screen, and a description of the study printed with the prescription. Physicians found the on-screen reminders unobtrusive and appreciated having the study information sheets to streamline explaining the study to their patients, and as take-home material.

Conclusion: Physicians found the reminders unobtrusive and felt that the reminders supported and streamlined the procedure of describing to their patients the opportunity to participate in a psychiatric treatment study. The use of electronic medical record systems at the point of care presents clinical investigators with an opportunity to identify and recruit study subjects within the flow of usual care.

Source of Funding: Supported by an investigator-initiated grant from GlaxoSmithKline

Session I – 23

A Comparison of Clinician vs. Electronic Monitoring of Antipsychotic Adherence in Schizophrenia

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Background: Assessment of medication adherence in schizophrenia has been limited by the availability of reliable, continuous measures in this population. Because they address many of the limitations of traditional adherence assessment tools, electronic monitoring devices have become the "gold standard" for assessing medication adherence in the study of general medical conditions and may offer similar advantages in patients with schizophrenia. The primary objective of this report was to evaluate the concordance of electronically-monitored (MEMS® cap) antipsychotic adherence with that determined by clinician-rated assessment among public sector outpatients with schizophrenia and schizoaffective disorder.

Methods: Antipsychotic adherence was determined monthly over 3 consecutive months by 2 different, independent methods: (1) electronic monitoring (MEMS®) caps, and; (2) Clinician Rating Scale, an ordinal scale of 1-7, with higher numbers representing greater adherence (blinded to MEMS® data). For MEMS® assessment, clinically meaningful non-adherence was defined as ≤ 70% during any 1 of 3 monthly evaluations. Clinically meaningful non-adherence was defined on the Clinician Rating Scale as a rating of ≤ 4 at any 1 of 3 monthly evaluations.

Results: Three consecutive months of MEMS® cap and clinician-determined antipsychotic medication adherence data were available for 21 patients. Meaningful non-adherence was more likely to be detected when assessment was determined by MEMS® cap (13/21) than the Clinician Rating Scale (1/21) (chi square=15.43, df=1, $p<0.0001$). Additionally, 7/21 patients were ≤ 50% adherent; 4/21 were ≤ 30% adherent, and; 3/21 were ≤ 10% adherent during at least 1 of the 3 monthly assessments based on MEMS® cap.

Conclusion: Electronic monitoring was a feasible tool to measure the antipsychotic medication adherence of patients in this study. Furthermore, MEMS® cap monitoring found high levels of clinically meaningful non-adherence among these public sector outpatients with schizophrenia and schizoaffective disorder during this brief, 3-month assessment period. Compared to electronic monitoring, clinician assessments dramatically underestimated antipsychotic medication non-adherence.

Source of Funding: Supported by the State of Texas' Mental Health Connections Research Program

Session I – 24

Use of Palm Pilot Technology to Collect Daily Parent Assessments of Evening and Morning Behaviors of Children with ADHD

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Background: Atomoxetine is efficacious in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) when administered once daily. Preliminary evidence suggests persistence of treatment effects into the evening when analyzing a parent paper diary used to collect children's home behaviors retrospectively over a week period. We wanted to confirm and extend these observations by assessing, in a more systematic and real time manner, efficacy during the evening and early morning hours. Additionally, we wanted to determine how soon after beginning treatment atomoxetine produces efficacy.

Methods: Children (n=197) with ADHD, aged 6-12 years, were randomized in a 2:1 ratio to eight weeks of once-daily atomoxetine or placebo treatment. Parents completed a daily questionnaire evaluating their child's behavior during the early morning and late afternoon/evening [Daily Parent Report of Evening and Morning Behavior – Revised (DPREMB-R)] beginning five days prior to randomization and for approximately four more weeks using an electronic entry system (PHT Esendant LogPad technology – PHT Corporation). Parents were instructed to rate the DPREMB-R each evening between 5PM and 12AM and transmit data daily by modem to the PHT server. Data for a particular day could only be recorded on that date. Remote monitoring of subject palm-pilot data in real time was conducted by the study sites and sponsor utilizing StudyWorks, a web-based software.

Results: An overall high level of compliance in DPREMB-R reporting was obtained. Eighty-eight percent (163 of 186) of parents met our most restrictive criteria, reporting at least 4 nights over a 5-day baseline period and at least 6 nights per week in one of the four post-baseline periods. Mean reductions in the DRPEMB-R total score and evening subscales were superior for atomoxetine-treated patients beginning the first day of dosing. At endpoint, mean reductions in the DPREMB-R total score and evening and morning subscales were superior for atomoxetine-treated patients.

Conclusion: Daily, electronic collection of the DPREMB-R using palm-pilot technology enabled us to capture real time data independent of the bias caused by recollection, and to show efficacy for atomoxetine beginning the first day of dosing. Real time monitoring resulted in a high level of compliance in DPREMB-R reporting.

Source of Funding: Eli Lilly and Company

Session I – 25

An Interactive Voice Response (IVR) Application to Predict Early Treatment Drop Out

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Introduction: Disorder severity, social stability, and personal motivation are predictors of treatment compliance and outcome. Cognitive functioning may also affect patients' compliance with treatment. An IVR testing program incorporating aspects of tasks like the Wisconsin Card Sorting Test (WCST), Paced Auditory Serial Addition Test (PASAT), and Trail Making Test (TMT) was developed to explore the potential for predicting early drop-out from treatment.

Methods: Adult subjects (N = 122) 18 yrs or older entering outpatient treatment for alcohol disorders were recruited for study participation. Data collection via touch-tone telephone occurred within seven days of treatment intake. Subjects were compensated $100 in gift certificates. Six weeks after intake subjects were classified as early treatment drop-outs if they: (1) failed to attend 2/3 of their appointments between Week 4 and Week 6; (2) withdrew from treatment AMA; or (3) were administratively discontinued from treatment by the provider. Machine learning methods (MLM) derived a scoring algorithm to distinguish treatment continuers from drop-outs in a "model development sample" of 91 (75%) subjects that was applied to the remaining 31 subjects (model validation sample).

Results: IVR task performances correlated significantly with established, validated neuropsychological measures. The treatment drop-out rate across the complete sample was 19%. Patient characteristics discriminating treatment continuers from drop-outs identified by the MLM in the development sample included dependence severity, PASAT performance, personal attitudes concerning the need for change, and prior treatment history. The scoring algorithm applied to the validation sample demonstrated acceptable sensitivity (83%) and specificity (76%) (Chi-square = 7.44, p.= .013). The scoring algorithm predicted twice as much drop-out as actually occurred, however.

Conclusion: This study supports the emerging research area of IVR-based neuropsychological assessment. Early treatment withdrawal is a barrier to effective treatment and a serious methodological concern in clinical trial studies. Accurate prediction of subjects most likely to drop out early would enhance development of possible preventive solutions.

Source of Funding: NIAAA grant 1R43AA12878

Session I – 26

Behavioral and Cognitive Effects of Pramipexole Augmentation for Patients with Schizophrenia or Schizoaffective Disorder

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Background: This study evaluated the effects of adding the dopamine D2/D3 partial-agonist pramipexole to atypical antipsychotics for patients with schizophrenia/schizoaffective disorder. Research suggests that pramipexole is helpful when added to conventional antipsychotics but not as a solitary treatment.

Methods: Twenty-four subjects (13 M, 11 F; 43.3 ±12.0 yrs.) with DSM-IV diagnoses of schizophrenia (n=7) or schizoaffective disorder (n=17) of at best moderate severity, taking stable doses of atypical antipsychotics (≥200 mg/day CPZ-equivalents, ≥4 wks.), were assigned to double-blind treatment with pramipexole or placebo over 12 wks. Titration was according to Parkinson's disease guidelines (0.375-4.5 mg/day over 6 wks. as tolerated).

Results: Only 2/11 (18.2%) subjects taking pramipexole vs. 4/13 (30.8%) taking placebo did not complete the protocol. Pramipexole use was associated with significant decreases in PANSS-total ($p<.044$) and -positive ($p<.006$; correlated with dose: $r_s = +0.730$, $p<0.026$). Preliminary analysis also suggests improvements in cognition. There were no significant differences in negative symptoms, mood, movement or prolactin effects. Treatment was generally well tolerated.

Conclusion: Pramipexole can be a safe and useful augmenting agent for patients with psychotic illness.

Source of Funding: Stanley Research Institute grant (to JPK); Bruce J. Anderson Foundation, and McLean Private Donors' Neuropsychopharmacology Research Fund awards (to RJB).

Session I - 27

The Equipoise Stratified Randomized Design (ESRD) in STAR*D: Increasing the Generalizability of Controlled Trials

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Background: STAR*D (Sequenced Treatment Alternatives to Relieve Depression) aims to define the most effective treatment strategies (e.g., augmentation or switch) and specific treatment options (e.g., medication A, B, C, or cognitive therapy) for patients not remitting with the first treatment (citalopram). However, patients vary in their willingness to accept either strategy and selected options, based in part on the degree of improvement and side effects encountered with the first step (citalopram). STAR*D employs a new research design (ESRD) to ensure patients are in equipoise about the treatment strategies and options to which they could be randomized following nonremission to citalopram.

Methods: All subjects are enrolled for up to 12 weeks of treatment with citalopram (Level 1). Upon exit from Level 1, patients are eligible to (a) discontinue the study, (b) enter follow-up - if at least a 50% reduction in baseline symptoms has occurred, or (c) continue in STAR*D in Level 2 which provides up to 4 switch treatments (sertraline, venlafaxin-XR, bupropion SR, or cognitive therapy) or up to 3 augment treatments (bupropion SR, buspirone, or cognitive therapy). Those intolerant to citalopram and those without a symptomatic remission (QIDS-C_{16}>5) are eligible for Level 2.

Results: Results to date indicate strong preferences among participants. Only 1% was willing to accept all 7 Level 2 treatments. Overall, most (49%) chose either a switch (medication and/or CT), or (36%) an augmentation (medication and/or CT). Only a minority (3%) selected to guarantee CT at Level 2 (i.e., CT switch or augment only). Based on the first 417 subjects to enroll into Level 2, the following acceptability strata were chosen:

3%	CT augment or CT switch
38%	All 3 medication only switch options
11%	All 4 switch options (3 medications and CT)
13%	All 3 augment options (2 medications and CT)
23%	All 2 medication only augment options (2 medications)

Conclusions: The ESRD ensures that the participants are in equipoise regarding treatments to which they could to be randomized. ESRD also assures that research results focus on the most commonly encountered clinical dilemmas, thereby maximizing both internal and external validity. Results to date indicate that participants are capable of making several sequenced choices in arriving at their decisions to select both treatment strategies and specific options.

Source of Funding: NIMH Contract N01-MH-90003

Session I – 28

Continuing Benefit of VNS Therapy Over 2 Years for Treatment-Resistant Depression

A. John Rush, M.D. [1], Mark S. George, M.D. [2], Harold A. Sackeim, Ph.D. [3], Lauren B. Marangell, M.D. [4], Mustafa Husain, M.D. [1], Ziad Nahas, M.D. [2], Sarah H. Lisanby, M.D. [3], James M. Martinez, M.D. [4]

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Background: Vagus Nerve Stimulation (VNS) has shown promising antidepressant effects in an open, acute phase pilot study of adults in a treatment-resistant major depressive episode (Rush et al, 2000, Sackeim et al, 2001, Marangell et al, 2002). Following one year of VNS therapy, observed case response rates increased from 31% to 45% and remission rates increased significantly from 15% to 27%, demonstrating that the acute antidepressant effects were largely sustained. We now report the effects of VNS therapy over 2 years with chronic or recurrent treatment-resistant depression.

Methods: Fifty-nine adult outpatients with chronic or recurrent depression in a treatment-resistant, non-psychotic major depressive episode received 2 years of VNS therapy including the 3-month acute study. Changes in psychotropic medications and VNS stimulus parameters were allowed during the long-term study. A priori response was defined as $\geq$ 50% reduction in baseline Hamilton Rating Scale for Depression (HRSD28) total score and remission as HRSD28 $\leq$ 10.

Results: Based on observed cases, response rates were 45% (25/55) at 1 year and 43% (18/42) at 2 years. Remission rates (observed cases) were 27% (15/55) at 1 year and 21% (9/42) at 2 years. A total of 8 patients have withdrawn and have been explanted. Two patients died, 1 due to sepsis, post colorectal surgery, and 1 due to lung cancer after withdrawing from the study and being explanted. The remaining 6 patients withdrew due to lack of efficacy or withdrawal of consent.

Conclusions: In this cohort of 59 patients with chronic or recurrent treatment- resistant depression, longer term VNS therapy was associated with sustained symptomatic antidepressant benefit in this naturalistic follow-up study.

Source of Funding: Grant support provided by Cyberonics Inc.

Session I – 29

Development of the Life Participation Scale for ADHD: An Adaptive Change Assessment Instrument

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Background: Increasingly, treatment providers and researchers note the importance of assessing adaptive functioning, quality of life, social development, emotion regulation, and other variables that better capture the emerging theoretical models of ADHD. Parents in recent clinical trials of atomoxetine reported improved adaptive and executive functioning that was not systematically assessed. While currently available measures assess some of the domains described by parents, none fully captured the improvements expressed. This dearth prompted the development of the Life Participation Scale (LPS) for ADHD.

Method: Based on the constructs identified in parent interviews, 110 items for a pilot semi-structured parent interview were created. To obtain expert panel validity, 4 other principal investigators reviewed and modified the pilot instrument. Following a second set of parent interviews, items that were redundant, commonly misinterpreted, confounded, or ambiguous were removed. The resulting interview of 34 items was included as a pilot instrument for 48 patients in a recently completed placebo-controlled clinical trial.

Results: The scale's sensitivity to change over time in a medication trial was demonstrated in this small pilot study (N= 48; $p<.10$), with the active group showing significant improvement from baseline (ATX $p<.001$; PBO $p=.27$). There was a trend toward statistical separation between treatment groups at endpoint ($p=.093$). Although there were no preplanned tests of construct validity in the clinical trial, the LPS showed evidence of both convergent and divergent validity with other measures included in the trial. The LPS was highly correlated with the Brown ADD Scale Total Score ($r=-.57$; $p<.001$), but was not correlated with the Child Health Questionnaire Bodily Pain subscale ($r=.04$; $p=.771$).

Conclusion: The Life Participation Scale for ADHD is a promising new instrument for assessing ADHD-related adaptive functioning in clinical trials and treatment settings.

Source of Funding: Supported by Eli Lilly and Company

Session I – 30

A Nursing Tool to Enhance Adherence and Recovery in Psychosis

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Introduction: Adherence to medications is a problem in medicine generally, and can be more compromised because of poor insight in patients with psychotic illnesses. Poor insight makes successful collaborations in treatment difficult and is an exceptionally troubling impediment to improvement. Increasing adherence and insight may enhance the potential for recovery. At present, there are few cost-effective strategies to improve insight in psychosis. We developed the Levels of Recovery from Psychotic Illnesses Scale (LORS) as a teaching tool for patients with psychotic illnesses. It is designed to identify strengths and weaknesses in insight in order to provide the basis for an intervention to enhance change and recovery. The State of Massachusetts Department of Mental Health Treatment Guidelines for Schizophrenia (1999) cites the LORS as an example of an educational tool for this population

Design and Methods: A pilot study to examine the feasibility of administering the LORS was conducted in 1999 at a community mental health center in Massachusetts with a total of 45 patients diagnosed with a psychotic illness. 52% of the subjects were men. The mean age of the subjects was 38 and on average they had been ill for 15 years**.** The LORS, a 13-item scale based on the PANSS, and the Behavior and Symptom Identification Scale (BASIS 32), a self-report of symptoms, were administered to all subjects initially, at 6 months, and at 12 months. Standard demographic data were collected as well. Pearson product moment correlations were calculated between the LORS factors and the 32 items of the BASIS 32.

Results: Two factors were identified in the LORS with a factor loading of at least .58, Need for Institutional Support, and Self-advocacy. These factors were significantly correlated (.661) with each other but no significant correlation was found with any of the BASIS 32 scores.

Conclusion: Preliminary data indicates that the two factors identified in the LORS are quite different from the symptoms that are rated by the BASIS 32 and other scales. Future research will be directed to identifying whether change in these aspects of patient functioning can contribute to improvement in adherence and potentially lead to recovery.

Source of Funding: Grant from NIMH/NINR Mentorship Program: Building the Capacity of Psychiatric Mental Health Nurse Researchers.

Session I – 31

Patient Perceptions of Quality of Life and Functionality in Panic Disorder: A Comparison of Venlafaxine XR, Paroxetine and Placebo

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Objective: To characterize patient-reported functionality and quality of life in panic disorder and compare treatment with venlafaxine extended-release (VEN XR), paroxetine, or placebo.

Methods: In a multicenter, randomized, double-blind, placebo-controlled trial, patients with DSM-IV panic disorder were randomly assigned to receive VEN XR (150 mg or 75 mg), paroxetine or placebo treatment for 12 weeks (N=577). Functional impairment was measured in terms of the work, social activities, and family life sub-scales of the patient-reported Sheehan Disability Scale (SDS) and quality of life in terms of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Baseline impairment and treatment-related improvement, at the last observation-on-therapy carried forward and the scheduled week 12 assessment, and adjusted for baseline score and center, on each of the SDS and Q-LES-Q components was evaluated.

Results: Overall, 68% of patients were "markedly" or "very severely" impaired in terms of social activities, 40% in terms of work, and 19% in terms of family life at baseline. VEN XR 150 mg was associated with significantly greater improvement, relative to placebo, at the scheduled week 12 and the final on-therapy evaluations on work (P=0.002 and P=0.003, respectively), social activities (P<0.001 and P<0.001, respectively), and family life (P<0.001 and P<0.001, respectively) sub-scales. Further, VEN XR 150 mg was associated with significantly greater improvement, relative to placebo, at both the final observation-on-therapy and the scheduled week 12 assessment on 7 of 10 sub-scales of the Q-LES-Q. Similar, albeit weaker, differences between active treatment and placebo were observed for VEN XR 75 mg and paroxetine.

Conclusions: Patient-reported quality of life and functionality are both recommended for measurement in panic disorder clinical studies by the National Institutes of Health Consensus Development Conference on Treatment of Panic Disorder. VEN XR was associated with significant improvement in improving both functionality and quality of life in patients with panic disorder.

Source of Funding: Wyeth Research

Reference:

1. Shear MK, Maser JD. Standardized assessment for panic disorder research: a conference report. *Arch Gen Psych.* 1994;51:346-354

Session I – 32

Benefits of Long-Acting Risperidone on Quality of Life in Previously Stable Patients with Schizophrenia

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Introduction: Although studies on the impact of atypical antipsychotics on health status in schizophrenia are limited, data suggest these agents offer such benefits. These and other benefits may be limited by the need for daily dosing. A long-acting atypical could offer further symptom improvement and functional gains. Treatment with long-acting risperidone was studied in this regard.

Methods: An open-label study assessed long-acting risperidone in 725 stable patients with schizophrenia/schizoaffective disorder. Patients were assigned by clinician's judgment to long-acting risperidone (25-75mg, every 2 weeks, 50 weeks). Efficacy was measured by PANSS and quality of life by SF-36. Data were stratified by prior antipsychotic use.

Results: At study entry, 336 (46.3%) patients were receiving oral risperidone and 188 (25.9%) conventional depots (27.8% received others). After receiving long-acting risperidone, mean PANSS total scores improved throughout the 50 weeks (both groups; $p<0.001$). There were improvements on SF-36 subscales for mental health, social functioning, and role emotional; these were significant for the prior risperidone group. Improvements in vitality and general health also occurred in both groups; these were significant for the prior depot group.

Conclusion: These results show substantial improvements with long-acting risperidone in functionality in patients previously stable with conventional depots or oral risperidone.

Source of Funding: Janssen Pharmaceutica Products, L.P.

Session I – 33

Cognitive Function in Patients with Alzheimer's Dementia During Double-Blind Treatment of Psychosis with Olanzapine

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Introduction: The efficacy of atypical antipsychotic medications in reducing psychotic symptoms is well established, but their potential effects on cognition in patients with Alzheimer's dementia (AD) are less well characterized.

Objective: To assess general changes in cognitive function in patients with Alzheimer's dementia (AD) during treatment with olanzapine or placebo.

Methods: Following a placebo lead-in period (≤14 days), 652 inpatients diagnosed with AD and delusions or hallucinations were randomly assigned to one of five treatment groups: placebo, or olanzapine at fixed doses of 1.0, 2.5, 5.0, or 7.5 mg/day, for up to 10 weeks of double-blind treatment.

Results: Patients' mean age was 76.6 years, and 75.0% were female. Mean latency from onset of dementia was 49.2±35.7 months. Mean Mini-Mental State Examination (MMSE) score was 13.7±5.1. At endpoint, mean MMSE scores (last observation carried forward) were increased slightly from baseline, significantly so in the 2.5-mg olanzapine group (+0.6±2.8, p=.019). Overall, however, no treatment-group comparisons with placebo were significant. Similarly, on the Severe Impairment Battery total scale, scores increased slightly from baseline in all treatment groups, significantly so in the placebo group (+1.8±8.0, p=.017), but no significant treatment-group differences were seen overall (p=.618). As adverse events, the incidences of confusion (0.7% to 0.8%, overall p>.99), sedation (0.0% to 1.5%, overall p=.230), and somnolence (0.8% to 3.8%, overall p=.261) were not significantly different among treatment groups, nor did any other treatment-emergent adverse events occur with a significantly higher incidence in any olanzapine group relative to placebo.

Conclusions: These data indicate that olanzapine at doses of 1.0 to 7.5 mg/day has no appreciable impact on cognition in elderly patients with AD.

Source of Funding: Eli Lilly and Company

Session I – 34

Subjective and Objective Indices of Cognition in Psychotic Versus Non-Psychotic Depression: A Report From CORE

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Background: Memory dysfunction and subjective reports of memory disturbance are common manifestations of psychiatric illness and may occur in the context of broader cognitive impairment. One factor that may predict actual or perceived cognitive impairment in depression is the presence or absence of psychotic features. There is a convergence of evidence suggesting that individuals with psychotic depression (PD) have more severe depressive symptoms, demonstrate more significant cognitive impairment, respond differently to specific treatments and, are more likely to have structural brain abnormalities than those with non-psychotic depression (NPD). This has led to the suggestion that PD may represent a different nosological entity than NPD. Differences in subjective reports of memory disturbance and their relationship to actual indices of cognitive status in psychotic versus non-psychotic patients, however, remain unclear.

Methods: The present study examined 125 psychotic and 262 non-psychotic unipolar depressed patients referred for ECT in the context of an ongoing collaborative study supported by the NIMH. Psychopathology and cognitive ratings were performed 24- 72 hours before ECT. Subjects did not differ with respect to age or sex. Patients were evaluated with the Hamilton Depression Scale (HAM-D), the Squire Subjective Memory Questionnaire (SSMQ), and the Modified Mini Mental Status Exam (MMSE).

Results: As expected, there were differences in severity of depressive symptomatology ($p<.0001$) with PD patients scoring significantly higher on the HAM-D. NPD patients exhibited more frequent complaints of memory disturbance on the SSMQ, which was inconsistent with actual test performance. In fact, NPD patients scored significantly higher on the MMSE ($p<.0001$) relative to PD patients. These differences remained even after adjusting for differences in education, age, and disease severity ($p<.0001$). There was a significant negative correlation between disease severity and the SSMQ. A significant inverse correlation was additionally evidenced between disease severity and the MMSE, but only in patients with PD.

Conclusion: These results suggest that PD and NPD individuals differ with respect to perception of cognitive status and actual level of impairment, which appears to be associated with the presence or absence of psychosis. These data further support the hypothesis that PD may be a distinct diagnostic entity.

Source of Funding: Supported by NIMH grants MH55484 (Rummans), MH55486 (Petrides), MH55489 (Husain) and MH55485 (Kellner)

* CORE: Consortium for Research on ECT

Session I – 35

Long-Term Cognitive Efficacy of Galantamine Is Not Affected by Patient Characteristics: A Continuance Analysis

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Background: Patients with Alzheimer's disease (AD) experience a gradual loss of cognitive and functional ability that may last for many years, leading up to death. Therefore, long-term therapy may be required for these patients. Galantamine is a novel cholinergic agent with a dual mode of action, acetylcholinesterase inhibition and allosteric nicotinic receptor modulation. In this study, we evaluated the sustained cognitive efficacy of galantamine treatment for 36 months in patients with mild-to-moderate AD.

Methods: This study was a 2-year, open-label extension of 2 double-blind, placebo-controlled clinical trials with open-label extensions. All patients entering the current trial had previously received a minimum of 6 months of galantamine treatment. In the current open-label phase, all patients received galantamine 24 mg/day for up to an additional 24 months (total potential galantamine exposure = 36 months). Change in cognition was measured by the ADAS-cog/11. Cognitive efficacy values of patients who completed the entire 36-month trial were statistically compared with the last 2 efficacy values for patients who withdrew from the study for any reason.

Results: ADAS-cog/11 scores of patients continuously treated with galantamine (10.2 ± 0.9 [SE]) increased more slowly over 36 months compared with the predicted increase of 20.5 to 22.0 points estimated by the Stern equation. Patients who completed the study ($n = 181$) were not statistically different from the overall study population, including those patients who had discontinued therapy for any reason ($n = 144$) ($p > 0.4$).

Conclusions: The cognitive benefits of galantamine are sustained for at least 36 months versus the expected decline in patients with AD. At endpoint, cognitive decline in galantamine-treated patients was delayed by approximately 18 months. This sustained clinical efficacy was not directly or indirectly affected by patients who discontinued from the study for any reason.

Source of Funding: Janssen Pharmaceutica Products, L.P.

Session I – 36

Maintenance of Cognition for 24 Months in Patients Treated with Galantamine for Probable Vascular Dementia

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Background: After Alzheimer's disease (AD), vascular dementia (VaD) is the second most common cause of dementia in the United States. Galantamine, a novel cholinergic drug with a dual mode of action (inhibition of acetylcholinesterase and allosteric modulation of nicotinic receptors), has demonstrated broad long-term benefits in patients with mild-to-moderate AD. Limited treatment options exist for patients diagnosed with VaD. The objective of this study was to investigate the long-term safety and efficacy of galantamine in probable VaD patients.

Methods: Patients with probable VaD or AD with cerebrovascular disease who completed a 6-month, double-blind, placebo-controlled study and a 6-month, open-label extension (OLE) were eligible to enter this 2-year, OLE trial with a fixed daily dose of galantamine 24 mg. Changes in cognition were assessed with the ADAS-cog/11. Data were analyzed in VaD patients at Month 12 of the OLE (total treatment duration: 24 months). Safety was evaluated as well.

Results: Of the 374 patients who completed the 2 previous trials, 326 entered the 2-year, OLE (135 had a diagnosis of VaD; of these, 60 had received galantamine continually for 24 months). Continuous galantamine treatment maintained cognitive levels at original baseline levels for 24 months (ADAS-cog/11 change from baseline: 0.8 ± 1.00 [SE]; $p = 0.407$). The most frequently occurring adverse events were those expected in an elderly population with dementia (depression, 13%; agitation, 12%; insomnia, 11%). The incidence of nausea and vomiting was lower than in the original double-blind study and 6-month OLE.

Conclusions: Long-term galantamine treatment is safe and effective in preventing cognitive decline for 24 months in patients diagnosed with probable VaD.

Source of Funding: Janssen Pharmaceutica Products, L.P.

Session I – 37

The Effects of Escitalopram Administered Alone and with Alcohol on Cognition and Psychomotor Performance

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Background: Escitalopram is a recently approved selective serotonin reuptake inhibitor for the treatment of depression. This study evaluated the effects of escitalopram alone and when co-administered with alcohol on cognitive and psychomotor function in healthy subjects.

Methods: This was a double blind, placebo-controlled study with a balanced 4X4 Latin square design. Nineteen healthy male subjects were randomly assigned to four sequence groups to receive the following treatments at weekly intervals: escitalopram alone (10 mg escitalopram + placebo alcohol), combination [10 mg escitalopram + alcohol (0.8 g/kg)], alcohol alone [placebo + alcohol (0.8 g/kg)], and placebo (placebo + placebo alcohol). Cognition and psychomotor functions were evaluated with a driving simulator, choice reaction time test, memory task, digit symbol substitution test (DSST), serial sevens, finger tapping test (FTT) and field sobriety tests. Subjective effects (eg. sedation) were rated by both the investigator and subjects. Blood alcohol concentrations (BAC) were measured through breath samples.

Results: Sixteen subjects (ages 21-31) completed the study. As expected, nearly all performance measures showed a significant impairment effect by alcohol alone ($p<0.05$). Escitalopram alone did not impair cognitive or psychomotor function relative to baseline measures and was comparable in effect to placebo on the psychomotor test battery except for the FTT where performance was significantly improved ($p<0.05$). When co-administered with alcohol, escitalopram did not further impair performance compared to alcohol alone but did significantly improve performance on the DSST, serial sevens and FTT ($p<0.05$) despite comparable BACs (peak: 0.08 gm%).

Conclusion: An acute dose of escitalopram given alone or with alcohol does not impair cognitive or psychomotor function in this study population.

Source of Funding: Supported by Forest Laboratories, Inc.

Session I – 38

A Spanish Verbal Learning and Memory Test for Use in Dementia Clinical Drug Trials

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Introduction: The methodological design of research studies must invariably examine the influence of demographic variables such as age, gender, and ethnicity. The rapid growth of Hispanics in the US has created a demand for culturally appropriate instruments to examine clinical change in relation to experimental interventions. This is particularly evident in research involving cognitive examinations since the measures utilized are vulnerable to cultural and ethnic influences. The Miami Attention and Memory Instrument (MAMI) was developed and standardized in 150 Hispanic subjects. This study examines the utility and clinical sensitivity of the List Learning subtest (L-L) of the MAMI in the assessment of verbal learning and memory in three groups of geriatric Hispanic subjects that were matched for age, gender, and education.

Methods: Participants were Spanish language dominant, born in the Caribbean and South-Central America that immigrated to the US as adults (>30 years of age). The three subject groups included: a) normal controls (NC, n=20); patients with Alzheimer's type dementia (SDAT, n=20); and patients with vascular dementia (VD, n=20). All NC subjects were determined to be cognitively intact and without clinical depression (Folstein MMSE $\geq$ 25 and BDI-II $\leq$ 8). The diagnosis of SDAT vs. VD was made by a board certified neurologist following a comprehensive neurological work-up. ANOVA procedures were performed to analyze the data.

Results: Our data revealed that both patient groups performed significantly below NC on the initial learning trial, total learning score, and immediate and delayed recall and recognition scores ($p<0.05$). Test results also revealed differences in the pattern and nature of the memory deficits present between the SDAT and VD subgroups. While both patient groups did not differ from each other on the total learning score, the SDAT group performed significantly below the VD group on measures of delayed recall and delayed recognition memory ($p<0.05$).

Conclusion: These findings indicate that the MAMI LL is a sensitive instrument that can be utilized in clinical research and drug studies that require the assessment of verbal learning and memory in geriatric Hispanic subjects that are primarily Spanish speaking.

Source of Funding: None

Session I – 39

The Treatment of American Hispanics with Antipsychotics: What Do We Actually Know?

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Justification: The U.S. Hispanic minority grew +60% in the last decade, and now numbers 35.3 million, 12.5% of the American population. However, Hispanics, like other minorities, are under-represented in drug clinical trials; neither do these trials analyze treatment efficacy within the group.

Objective: Review the information available on the treatment of American Hispanics with antipsychotics, draw some conclusions, discuss them, and make some proposals for the pharmacogenomic era of psychiatry.

Method: A review was made of all published studies regarding treatment of Hispanic Americans with antipsychotics, both typical and atypical, using Medline and the references from available publications. Two other reviews, on the pharmacokinetics of antipsychotics in Hispanics and the characteristics of clinical investigation with Hispanics, were also done for the discussion.

Conclusions: 13 studies that allow some conclusions on the treatment of Hispanics with antipsychotics were found. They are retrospective and several have size or method limitations. However, some trends are perceived: in spite of no obvious differences in response rates or side effects, Hispanics tend to receive lower doses of antipsychotics, less atypical antipsychotics and more depot antipsychotics.

The role of socioeconomic vs cultural/ethnic factors in the genesis of these differences needs to be ascertained. The dose differences are not accounted for by our current knowledge of pharmacokinetics in Hispanics.

Some suggestions are discussed in order to make sure that Hispanics as a group benefit from the current pharmacogenomic progress in psychiatry. These include normative issues and practical steps regarding clinical investigation with Hispanics.

Source of Funding: None

Session I – 40

Clinical Characteristics of Depression in African American Primary Care Patients

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Ethnic scholars have long claimed that depression is under recognized and under diagnosed in African Americans. Reviews of the literature are confusing, with comparisons of the racial/ethnic groups showing the same, greater or smaller prevalence rates, even when socio-economic factors are controlled. Some of the more widely used epidemiological diagnostic screening scales appear to be culturally biased. The CES-D seems to be more sensitive in detecting caseness of depression in African Americans, especially women. We have been attempting to assess short, easy to administer and score, and most importantly, culturally competent screening tools for detecting depression in African Americans in our busy primary care centers.

Adult African American clients were approached at the Family Practice Center (FPC), the study explained, and informed consent obtained. Participants provided demographic data, SES and completed the SF-36 and the SDS (n=287) [April-August 2000] or the SF 36 and the CES-D-R (September 2000 - present; n=780). The FPC cohort represents a well-educated group, with over 70% having some post graduate vocational training or some college, most were insured. FPC serves predominantly adult and middle-age clients, with less than 7% 60 years or over.

Results from the screening scales revealed that 30% of participants reported clinically significant depression, but less than 20% of the participants reported feeling “sad” or “depressed” most of the time. Anhedonia, lassitude, insomnia and bodily pain were reported much more frequently. We have now amassed quality of life data (SF-36) on more than 1500 African Americans with 10 commonly occurring chronic illnesses. Depression is the most debilitating chronic illness observed. More than half of clients with either diabetes or hypertension are clinically depressed. Increased morbidity was reflected in increased burden of illness in both physical and mental domains when depression is present. Less than 5% of the depressed patients were being treated for their depression.

African Americans seldom report “typical” symptoms of depression, such as feeling sad or depressed. Anhedonia (not getting pleasure out of life anymore) and lassitude (no get up and go/low energy), insomnia, and bodily pain were much more common. We propose the infrequent reports of clearly recognizable “typical” depression symptoms coupled with the high frequency of physical symptoms play a role in the low recognition of depression by primary care givers. Any instrument used to screen for depression in this population must take that into account. We have initiated a depression referral system within the FPC which includes physicians trained in the treatment of depression and sychopharmacology, various councilor and non-drug options, and psychiatric-provided services and referrals.

Source of Funding: Research supported by MH58647 (MRISP) and the Center for Minority Health and Health Disparities.

Session I – 41

Alternative Medicine Use in Native American and Hispanic American Veterans with and without Axis I Diagnoses

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Background: The use of alternative medicine, in particular herbal remedies, is very prevalent among psychiatric outpatients but there is limited information about its use among minorities. In the present study we explore the use of herbal remedies in a sample of American Indians (AI) and Hispanic American (HA) veterans in New Mexico. The aims of the study were to 1) explore the use of herbal remedies used in these two ethnic groups and 2) investigate the effect of any axis I diagnoses on herbal use.

Methods: 780 participants were enrolled using non-probability sampling. Evaluation included the computer-based Quick Diagnostic Interview Schedule (Q-DIS) to provide current and lifetime axis I diagnoses; the 57-item Brief Symptom Inventory derived from the SCL-90; Modified Michigan Alcohol Drug Screening Test and Modified PTSD Checklist (PCL-M). 487 participants completed a questionnaire about lifetime and recent use of alternative medicine for medical and psychiatric reasons.

Results: 56% reported ever taking herbs or supplements. There were no differences between subjects that reported use of herbs and those that did not on: level of education, ethnicity, serving in combat or marital status. Subjects that answered yes were more likely to have a diagnosis of posttraumatic stress disorder or depression. The following reasons were reported for taking supplements: 46% for a medical condition, 34% to improve energy, 24% to improve sleep, 23% for anxiety and 14% for depression/sadness. Only 35% informed their doctors of use of herbs.
AI participants were more likely than HA to take herbs for a psychiatric condition, depression or anxiety. AI were also more likely to talk with a healer over the last year.

Conclusion: The use of herbal remedies is highly prevalent in AI and HA veterans. Most patients take herbs for medical reasons and the majority do not tell they doctors about this use. AI report more use of herbs for psychiatric reasons. Veterans with PTSD and depression were more likely to use herbal remedies.

Source of Funding: HSR&D Office of the Veterans' Administration

Session I – 42

Major Depression Among Minority Patients with Osteoarthritis: Prevalence and Response to Pain Treatment

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Background: Previous studies of depression in patients with osteoarthritis have been limited by small samples and the lack of diagnostically valid measures. The goal of this analysis was to evaluate the prevalence of major depression among ethnic minority patients with osteoarthritis before they were enrolled in a pain treatment trial.

Methods: African American, Hispanic, and Asian patients with osteoarthritis of the knee were enrolled in three separate and identically designed six week multicenter, randomized, double-blind parallel controlled studies with flexible dosing of celecoxib, naproxen, or placebo. The targeted enrollment for each study was 300 patients. The PHQ-9, a 9 item validated measure for depression assessment in primary care settings was used at screening evaluation. Scores $\geq$ 10 have a 88% sensitivity and specificity for DSM-IV major depression. Preliminary analyses with over 85% of the target enrollment are cited below.

Results: 294 African Americans, 288 Hispanics, and 255 Asians were available for analysis. The mean PHQ-9 by group ranged from 3.1 (sd 4.3) to 6.2 (sd 5.5), with Hispanics having the highest mean score. Using a PHQ-9 cut off score of $\geq$ 10, 23.8% of African Americans, 22.9% of Hispanics, and 10.2% of Asians had major depression. Among patients that reported any depressive symptoms, 50.7% of African Americans, 45.8% of Hispanics, and 32.5% of Asians reported that the symptoms made it difficult to carry out normal daily functions.

Conclusion: Major depression is highly prevalent among minority patients with osteoarthritis and is associated with functional burden. Clinicians are advised to screen for depression among these patients and monitor their symptoms during pain treatment

Source of Funding: Pfizer, Inc.

Session I – 43

Correlates of Self-Reported Physical Health and Health Behavior Among Caregivers of Patients with Bipolar Disorder

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Objective: The experience of burden among dementia and schizophrenia caregivers has been associated with adverse physical health. We investigated the physical health and health behavior of caregivers of patients with bipolar disorder in relation to subjective burden and illness coping.

Methods: 106 primary caregivers (PCs) of patients with SCID-diagnosed bipolar disorder enrolled in the naturalistic treatment study, (Systematic Treatment Enhancement Program for Bipolar Disorder, STEP-BD; Gary Sachs, M.D., P.I.) were interviewed at study admission on measures of subjective burden, health risk behavior, illness appraisal/coping, and medical status. Hierarchical regression models were run to evaluate the contribution of burden and coping to degree of health risk behavior and number of medical conditions reported, after controlling for PC demographics and patient history.

Results: The commonest health risk behaviors were: not enough rest (57%) or exercise (45%); 25% put off medical care, 13% forgot prescription medication. Subjective burden explained 28% additional variance in health behavior beyond that explained by demographics and patient history ($p < .0001$): More burdened PC's engaged in riskier behavior. Coping explained 15% additional variance (final adjusted $R^2 = .457$): Perceived patient control was associated with increased, and PC mastery with decreased health risk behavior. 60.4% PC's reported 1+ medical conditions; 33.9% reported 2+. The most frequent conditions were: hypertension (32%), arthritis (31%). Subjective burden marginally increased the variance explained in medical conditions beyond that explained by demographics/patient history ($p = .06$). Coping explained 16% additional variance (final adjusted $R^2 = .314$): Perceived social support was associated with decreased number of conditions.

Conclusion: Although caregiver burden is associated with poor physical health and health risk behavior in bipolar disorder, improved coping may help ameliorate these adverse effects.

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Session I – 44

Use of Venlafaxine for Chronic Pain Associated with Post-Herpetic Neuralgia

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Introduction: Several reports have provided evidence of the use of venlafaxine, a serotonin-norepinephrine reuptake inhibitor, as an analgesic agent in both animal and human experimental pain models and in various clinical conditions. We report here the results of an exploratory, randomized, placebo-controlled clinical trial to further evaluate these attributes of venlafaxine in the treatment of the chronic pain associated with post-herpetic neuralgia.

Methods: A total of 135 patients meeting clinical criteria for chronic pain associated with post-herpetic neuralgia were enrolled for study and provided clinical data for analysis. Patients were randomized to 6 weeks of treatment with either placebo or venlafaxine extended release capsules (75-225 mg QD). Efficacy was evaluated by measuring pain intensity using the standard technique of visual analog scales (VAS-PI). Safety was assessed by spontaneous adverse events and laboratory measures.

Results: A total of 12 patients withdrew from the study due to adverse events, 10 venlafaxine-treated patients and 2 on placebo. VAS-PI scores were examined using LOCF technique and showed a numerical, but not statistically significant advantage for venlafaxine compared to placebo treatment (mean adjusted change from baseline: -15.5 mm v –14.0 mm).

Conclusions: Combined action of norepinephrine and serotonin have been implicated as key mediating neurotransmitters in the perception of chronic painful events. Several reports have provided evidence of venlafaxine's clinical analgesic effect consistent with this view.

Source of Funding: Wyeth Research

Session I – 45

Impact of Comorbid Diabetes and Schizophrenia on Healthcare Resource Use

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Introduction: We compared use of healthcare resources in people with schizophrenia alone, comorbid diabetes and schizophrenia, and diabetes alone.

Methods: In June 2002, 850 people with schizophrenia, identified through NAMI and CMHCs, completed self-administered questionnaires. Of these, 109 (12.8%) reported comorbid diabetes. For comparison, a random sample of 1,000 type 2 diabetic individuals (18-64 years old) was generated from a similar study of 4,721 people with diabetes. Data on ER visits and hospitalization during the past 6 months were collected for all respondents. Costs were calculated using *Statistical Abstracts of the United States: 2000*, resulting in estimates of $320 per ER visit and $1,126/day for hospitalizations. Gender, age, and race were controlled using multiple regression analysis.

Results: People with schizophrenia averaged 3.3 days more hospital time ($p=0.004$) than patients with diabetes alone (additional cost $3,700). People with comorbid schizophrenia and diabetes averaged 1.2 more ER visits ($p<0.001$) and 11.3 more hospital days ($p<0.001$) than patients with diabetes alone (additional costs $396 and $12,800, respectively), and 1.0 ER visit more ($p=0.001$) and 8.1 more hospital days ($p\leq0.001$) than respondents with schizophrenia alone (additional costs, $319 and $9,100, respectively).

Conclusion: Comorbid schizophrenia and diabetes are associated with significantly greater healthcare resource use and costs of care than diabetes or schizophrenia alone.

Source of Funding: Pfizer, Inc.

Session I – 46

Patient Expectation as a Predictor of Outcome in Antidepressant Treatment

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Background: There has been little systematic study of the relationship between patient expectations of improvement and outcome of the pharmacological treatment of depression. This study was conducted to examine subject expectations for treatment and other potential predictors of treatment response.

Methods: 25 subjects meeting DSM-IV criteria for major depression with Ham-D $\geq$ 17 were enrolled in a treatment trial using reboxetine. Following a one week single-blind placebo lead-in, subjects were treated for eight weeks with reboxetine 8 - 10 mg per day. At the initiation of this study, subjects were asked to report their expectations for the effectiveness of the medication that they were about to receive. Forced-choice responses were "not at all", "somewhat", or "very effective." Associations between the subject's expectation and their response to treatment were examined, using a response criteria of final Ham-D < 10.

Results: Subjects with a higher pretreatment expectation of improvement had a greater likelihood of response. Of the subjects who reported their expectation that the medication would be "very effective" 90.0% responded (n=9), while only 33.3% of those who reported "somewhat effective" responded (n=5) [X^2=7.819 p=.005]. There was no association between the initial level of depression severity, duration of current episode, number of prior episodes, or basic demographic factors and outcome.

Conclusion: These findings suggest that individuals with high baseline expectation of improvement demonstrate a significantly higher level of response to reboxetine, an experimental antidepressant compound, than those with a lower expectation of improvement with treatment.

Significance: Subject expectation should be examined as a predictor of outcome in pharmacologic treatment trials, and may account for heterogeneity in treatment effectiveness. Future research should examine methods for altering expectations to determine if this can affect response rates in clinical trials.

Source of Funding: A grant from Pharmacia and Upjohn.

Session I – 47

Menopausal Status in Major Depressive Disorder Treated with Fluoxetine

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Objective: to assess the impact of menopausal status on treatment-response, in a cohort of outpatients with major depressive disorder (MDD) treated with fluoxetine.

Methods: Outpatient women with a SCID-diagnosis of MDD (DSM III-R criteria) aged 18 to 65 years were treated openly with fluoxetine (20 mg/day) for 8 weeks. The 17-item Hamilton Depression Rating Scale (HAM-D-17) was administered at baseline, and at weeks 2, 4, 6 and 8. Remission and response of depression were defined as a HAM-D-17 score ≤7 and a HAM-D-17 decrease ≥50%, respectively. Post-menopausal status was defined as amenorrhea for ≥1 year or use of hormone replacement therapy (HRT) for ≥1 year (among women aged ≥45). Patients were classified as peri-menopausal if aged ≥38, presenting with at least moderate hot flashes/ sweating, and irregular cycles or recent amenorrhea (≤1 year). Patients were considered pre-menopausal if aged ≤37, without significant vasomotor symptoms or menstrual irregularity. Pre- vs. peri- post-menopausal status, severity of depression and of menopausal symptoms were tested as predictors of remission and of time to response by Logistic Regression Analysis and Cox Proportional Hazard Model, respectively (intent-to-treat and completers analyses).

Results: A total of 184 women (pre- [n=121], peri- [n=28], and post-menopausal [n=35]) were included in the analyses. Overall mean age: 39.4±10.7. The mean HAM-D-17 score at baseline was 19.8±3.3 vs. 20.2±3.1 (t-test, p=ns) in pre-menopausal and peri- post-menopausal women, respectively. Remission rates at endpoint were similar in the two groups, 50% (pre-) vs. 44% (peri- post-; Fisher' exact test, p=ns); time to response was 5.9±2.2 vs. 6.0±2.1 weeks (t-test, p=ns). Neither menopausal status (coef -.096; χ^2=.064; p=.80) nor severity of menopausal symptoms (coef -.011; χ^2=.012; p=.91) predicted remission or time to response. Completers analyses held similar results.

Conclusion: In our study on MDD, menopausal status did not affect significantly the antidepressant response with fluoxetine. These findings are consistent with the negative study by Amsterdam and colleagues (1999) on the correlation between response to fluoxetine and use of HRT, in depressed women aged ≥45. Future studies should investigate the putative correlation between response to SSRIs and plasma levels of estrogen (physiologic or HRT-induced) in depressed women.

Source of Funding: Supported in part by NIMH grant R01-MH48483 (Dr. Fava)

Session I – 48

Retrospective Cohort Study of Diabetes Mellitus and Antipsychotic Treatment in a Geriatric Population in the United States

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This analysis investigates the risk of developing diabetes mellitus among elderly patients aged 60+ during treatment with antipsychotic medications.

Diabetes risk was studied by analyzing new prescription claims for antihyperglycemic agents in the AdvancePCS claim database among elderly patients who initiated antipsychotic therapy within a 3-month period. The following cohorts were studied: (1) an elderly reference population [no antipsychotics used: *n*=1,836,799], (2) all conventional antipsychotics [*n*=11,546], (3) haloperidol [*n*=6481], (4) thioridazine [*n*=1658], (5) all atypical antipsychotics [*n*=19,407], (6) clozapine [*n*=117], (7) olanzapine [*n*=5382], (8) quetiapine [*n*=1664], and (9) risperidone [*n*=12,244].

The incidence of new diabetes was higher in every antipsychotic cohort than in the standard reference population. Risks were not different overall, however, between the atypical and conventional antipsychotic cohorts (2&5). For the individual antipsychotic cohorts, risk was highest for patients treated with thioridazine (95% CI: 3.1–5.7) and lowest for quetiapine (95% CI: 1.3–2.9). Risks for the haloperidol, olanzapine, and risperidone cohorts were intermediate. Among atypicals, only patients treated with risperidone had a significantly higher risk (95% CI: 1.05–1.60, *p*=.016) than haloperidol. Conclusions about clozapine were hampered by the low number of patients in the cohort.

Although causality remains to be demonstrated, diabetes risk was higher among elderly patients receiving antipsychotic treatment than among the general elderly patient population. As a group, risk for atypical antipsychotics was not higher than for conventional antipsychotics, but risperidone's risk uniquely was significantly higher than haloperidol's.

Source of Funding: Eli Lilly and Company

Session I – 49

Prospective Evaluation of Insulin Sensitivity by the Hyperinsulinemic, Euglycemic Clamp in Healthy Volunteers Treated with Olanzapine, Risperidone or Placebo

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Objective: Cases of new-onset diabetes or exacerbation of pre-existing diabetes have been reported for patients receiving atypical antispychotics. Drug-induced insulin resistance may be a potential mechanism linking these medications to dysglycemia. The primary objective of the current study was to determine if treatment with olanzapine or risperidone was associated with a decrease in insulin sensitivity.

Methods: This was a prospective, randomized study to assess insulin sensitivity in healthy volunteers using a two-step hyperinsulinemic, euglycemic clamp. Blood glucose values were clamped at ~ 90 mg/dl and insulin was infused at rates to produce serum insulin concentrations that approximate the half-maximal and maximal concentrations for stimulation of peripheral glucose uptake. Glucose regulatory mechanisms were also assessed using a two-meal Mixed Meal Tolerance test (MMTT). Subjects were studied at baseline and again after 21-23 days of treatment with olanzapine (10 mg/day), risperidone (4 mg/day), or placebo. Subjects were admitted to an inpatient facility for 3 days prior to the baseline assessments. Following baseline assessments, subjects were randomized 1:1:1 to olanzapine, risperidone, or placebo treatments. Subjects were allowed up to three 72-hour outpatient passes during the active therapy period but were readmitted for 24 hours prior to the final assessments. Investigators performing the metabolic studies were blinded to treatment.

Results: Using a two-step hyperinsulinemic, euglycemic clamp, no significant changes in glucose disposal rate were observed in any treatment group. There was also no change in insulin sensitivity following treatment with olanzapine or risperidone. Small changes in glucose and insulin levels were noted during the MMTT. In general, the directions of the changes were similar between the olanzapine and risperidone or placebo groups.

Conclusion: Overall, this study failed to demonstrate that treatment of healthy volunteers with olanzapine or risperidone significantly affects insulin sensitivity or peripheral tissue glucose uptake. Results of this study do not support the hypothesis of direct drug-induced insulin resistance.

Source of Funding: Eli Lilly and Company

Session I – 50

Fasting Lipids in Normoglycemic Patients with Schizophrenia

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Objective: To examine fasting lipid levels in patients with schizophrenia

Methods: Cross-sectional measurement of fasting lipid profiles in normoglycemic (FBS < 110 mg/dl) patients with schizophrenia treated continuously for ≥1 year with olanzapine (n=67), risperidone (n=65), or typical (n=52) antipsychotics.

Results: Overall, the 3 treatment groups were well matched in number of normoglycemic patients completing the protocol as well as for physical, psychiatric, and historical characteristics. No significant differences were seen in mean total cholesterol, LDL cholesterol, LDL particle size, HDL cholesterol levels or total cholesterol/HDL ratio among patients matched for gender, BMI, duration and severity of psychiatric illness in the three treatment groups. LDL particle concentration, apolipoprotein B, and fasting (natural log transformed) triglyceride levels were significantly higher in the olanzapine group compared to risperidone but not compared to typicals. The HOMA-IR (insulin sensitivity) and predicted 10-year coronary heart disease risk (Framingham model) were also not significantly different among therapy groups.

Conclusions: No significant differences in cholesterol levels, insulin sensitivity, or predicted 10 year CHD risk were seen among treatment groups. Chronic treatment with olanzapine was associated with higher triglyceride levels and some qualitative differences in the LDL subfraction compared to matched patients receiving risperidone.

Source of Funding: Eli Lilly and Company

Session I – 51

Fasting Glucose Lipids and Leptin Levels and Glucose Tolerance Tests in Patients Treated with Olanzapine, Risperidone, Clozapine, or Conventional Antipsychotics

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Background: There have been contradictory reports of the tendency of atypical antipsychotics to induce type 2 diabetes and related glucose (GLU) and lipid abnormalities. Most studies have been based on drug prescription data bases or medical chart data collected for other purposes, and not fasting measures of relevant chemical measures combined with glucose tolerance tests.

Method: We are conducting a cross-sectional study of fasting measures of glucose and lipids, and glucose tolerance tests (GTT) in all patients with fasting glucose ≥110 mg/dl, in 200 patients with schizophrenia who were not being treated with antidiabetic drugs. Patients were treated with conventional antipsychotics (TYP), olanzapine (OL), risperidone (RIS), or clozapine (CL) as their only antipsychotic. Additional GTT's were performed on a sub-sample of patients which fasting glucose <110 mg/dl.

Results: Analyses to date in 189 patients showed that there were few consistent differences in mean fasting chemical values among the four antipsychotic drug groups. In the main analyses ANOVA'S showed significant (P<.05) between-group differences for leptin and triglycerides, which also held when BMI was controlled for as a covariate. Turkey HSD comparisons showed mean values of leptin higher in RIS than OL groups (P<.05), and a trend for mean values of triglycerides higher to be higher in the Cl and OL groups (P<.10). With additional background factors controlled for, there were no significant differences in mean values among the 4 groups in: glucose, glycohemoglobin, insulin, c-peptide, fructosamine, cholesterol, triglycerides, HDL, LDL, chol/HDL ratio, leptin. Patients on CL and OL had a higher number of subjects with triglyceride values above the 249 mg/dl level. 3 RIS patients had fasting GLU ≥126 mg/dl; none of the other drug groups had patients with fasting GLU ≥ 126ng/ml. GTT performed in patients with fasting GLU ≥ 110 mg/dl were abnormal in: 6 RIS patients, 2 CL patients, none of 3 OL patients, and 1 of 3 TYP patients. ANOVA 's showed 1 and 2 hr GTT GLU levels significantly (P<.04) higher in RIS than OL patients. GTT tests performed on a subset of patients with normal fasting GLU levels (i.e., <110 mg/dl), did not show abnormal GTTs, suggesting that our failure to have GTT tests in all patients did not produce an underestimate of glucose abnormalities. However, RIS tended to have higher (P<.10) 1 hr glucose levels than OL patients. There were small non-significant trends for RIS patients to have higher mean fasting insulin and glycohemoglobin levels.

Conclusions: Our results support the conclusion that there are not marked differences in hyperglycemia indices among hospitalized chronic schizophrenic patients treated with different atypical or conventional antipsychotics; in our sample there was a greater degree of abnormalities on some glucose and leptin indices in RIS patients and triglycerides in clozapine and olanzapine patients.

Source of Funding: Supported by an Independent Investigator Grant from Eli Lilly Pharmaceuticals to Dr. Smith (PI).

Session I – 52

Olanzapine Induced Reductions in Frontal Lobe Lactate Levels Correlate with Treatment Response in First Episode Psychosis

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Purpose: Typical and atypical antipsychotic medications differ in the extent to which they inhibit respiratory enzyme activity, with typical neuroleptics producing greater degrees of inhibition. Lactate is a neurochemical marker that increases with mitochondrial dysfunction and can be detected using proton magnetic resonance spectroscopy (1H MRS). We hypothesized that olanzapine (Olz) treatment would result in a greater reduction of brain lactate levels than haloperidol (Hal) treatment in subjects with a first episode of psychosis.

Design: Subjects with a first episode of psychosis (N=263) were randomized in a multi-site, double-blind treatment trial to either Olz or Hal. Single voxel, 6 cm3, 1H MR spectra of the left frontal lobe (FC), basal ganglia (BG), and hippocampal (HC) regions were acquired before and following 12 weeks of treatment for 156 subjects. The weak lactate doublet at 1.4 PPM was fit using an automated fitting method and the intensity of this resonance was normalized using a replacement phantom.

Results: An acceptable fit of the lactate resonance was obtained for 81 study subjects. After 12 weeks, mean lactate reductions in the FC, BG, and HC were 12%, 18%, and 13% for the olanzapine cohort and 1%, 3%, and 8% for the Hal cohort (n.s.d.). Reductions in frontal cortex lactate were strongly correlated with reductions in PANSS (ρ=0.357, p=0.0011) and BPRS scores (ρ=0.344, p=0.0017) for the entire subject population and for the Olz cohort (ρ=0.441, p=0.0035 and ρ=0.367, p=0.017, respectively; N = 42). These correlations were much weaker in the Hal cohort (ρ=0.225, p=0.17 and ρ=0.326, p=0.043, respectively; N=39).

Conclusions: Reductions in frontal cortex lactate during Olz treatment appear associated with resolution of psychotic symptoms. This relationship is numerically weaker with Hal treatment, which has been associated with inhibition of complex 1. Lactate appears to be a chemical marker for the frontal hypometabolism that has been reported in prior studies; strategies to reduce brain lactate levels may present novel therapeutic opportunities for the treatment of schizophrenia. These findings are also consistent with the lower incidence of depression associated with olanzapine therapy, as we have recently observed elevated brain lactate levels in depressed, unmedicated bipolar subjects.

Source of Funding: Eli Lilly and Company

Session I – 53

Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC): Rationale and Design

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Objective: ZODIAC is an open-label postmarketing study designed to compare cardiovascular safety of ziprasidone and olanzapine in a large simple trial. Unprecedented in size and design, ZODIAC's primary objectives are to estimate relative all-cause, nonsuicide, suicide, cardiovascular, and sudden death mortality among ziprasidone and olanzapine users. Secondary objectives are to estimate relative incidence of all-cause hospitalization and hospitalization for arrhythmia, myocardial infarction, or diabetic ketoacidosis, and of treatment discontinuation.

Methods: ZODIAC is now recruiting 18,000 patients from various treatment settings in the US, Sweden, and Brazil. After enrollment, brief information, including demographics, disease severity, cardiac risk factors, and prior antipsychotic medication use, is collected on a baseline questionnaire. Following random assignment of medication (1:1), no further study-related interventions, tests, or visits are required. Physicians and patients may change regimens and dosing of assigned study medication, and concomitant medications are permitted. Patients are followed as clinically appropriate and outcomes are assessed for up to 1 year. Information on patients' vital status and hospitalizations is obtained through follow-up. External scientific committees will provide study oversight and blinded assessment of events.

Conclusions: ZODIAC's size provides the power to evaluate small risks, its simplicity minimizes the artificiality imposed by premarketing studies, and random allocation provides for unbiased group comparisons.

Source of Funding: Pfizer, Inc.

Session I – 54

NIMH Comparative Effectiveness of Antipsychotic Medications in Patients with Alzheimer's Disease (CATIE – AD): A Progress Report

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The NIMH-sponsored *Clinical Antipsychotic Trial of Intervention Effectiveness – Alzheimer's Disease* (CATIE-AD) is a multicenter effectiveness trial, assessing multiple outcomes over 9 months in 450 outpatients with AD who might benefit from atypical antipsychotics. The sequential 'hybrid' design combines elements of efficacy trials with effectiveness trials to assess the comparative outcomes of risperidone, olanzapine, and quetiapine, and, at a second level, the likelihood of response to a subsequent antipsychotic or to citalopram in patients who did not respond to initial treatment. The trial is designed to model clinical practice, requiring considerable involvement by the clinician-investigator with respect to treatment decisions regarding randomized and double-blinded medications. Its design takes advantage of the uncertainty principle and the concept of clinical equipoise in assessing the non-superiority of the intervention algorithms.

In this presentation we will first describe the protocol, barriers to recruitment, inter-site variability, and the characteristics of the first 267 patients randomized. Their age range is 52-105 years (mean 78.0); 57% are female; 58% are married; 33% are widowed, 72% are living at home; 8% are living in an assisted living facility; and 20% are minorities. Participants represent the full range of dementia severity with a mean MMSE of 14.5. About 25% are severely, two-thirds are moderately, and the rest mildly demented. Our presentation will also highlight some of the variations in clinical practice and clinical research encountered in this trial, such as relatively brief periods of medication exposure prior to switching therapies.

Session I – 55

Affective Deficits in Schizophrenia and in Depresssion

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Background: Flat affect is present in 66% of patients with schizophrenia, is the only universally accepted negative symptom, and is best understood as a deficit in the expression of emotions, an "encoding" deficit. However two major questions remain unresolved: its specificity (depressed patients may show blunt affect) and its delineation (deficits in expression of emotions only or in overall expressiveness). Schizophrenia research has focused on expressions of emotions, and not on other non-verbal meaningful expressions such as illustrators or emblems.

Methods: 58 non-depressed inpatients with schizophrenia, 25 inpatients with major depression without psychotic features and 25 normal controls underwent three tests. First, subjects were asked to imitate facial emotional expressions shown on pictures. Secondly, subjects were told to show a specific emotion in their faces. In the last task, subjects were asked to describe an event related to a specific emotion. Patients were videotaped. One blinded examiner rated facial emotional expressions with the FACS. Another blinded rater counted the number of illustrators. Clinical ratings were obtained for all patients.

Results: Compared to normal controls, patients with schizophrenia and patients with depression expressed the expected emotions less frequently in the three tests, and they expressed less social smiles and illustrators. Differences in emotional expressions between schizophrenia group and depression group did not reach significance for the 3 tests. Patients with schizophrenia expressed less illustrators than patients with depression. However, after controlling for number of words, this difference did not held.

Discussion: Affective deficits include deficits in various domains: volitional expression of emotions, spontaneous (or semi-spontaneous) expression of emotions, social smiles, and non-emotional meaningful facial expression. When compared to depressed patients, affective deficits of patients with schizophrenia are not different in all these domains, but alogia interferes with the rating of affective deficits. Non-depressed patients with schizophrenia and patients with current depression show similar affective deficits (in their nature and degree). Therefore, the major component of deficits in affect expression is not the affective one, but the expressive one, i.e. the neuromotor one. Affective deficits may just be one special aspect of the motor deficits seen in schizophrenia and in depression.

Source of Funding: New York State Psychiatric Institute Internal Grant.

Session I – 56

Comorbid Psychiatric and Health Problems in a Sample of Black and White Women Presenting to a Cardiac Emergency Room with Negative Chest Pain Results

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Background: The increasing emphasis on identifying and reducing healthcare disparities among racial, ethnic, low socioeconomic status and other vulnerable populations is driven by research that examines these factors either directly or indirectly. This poster presents comorbidity data derived from two hypotheses in the study: Blacks And Whites Presenting To A Cardiac Emergency Room With Negative Cardiac Test Results: Evaluation For Panic Disorder And Other Comorbid Health Problems. The objective of the study was to describe the population of patients who presented to a University Hospital Chest Pain Center evaluated for the presence of panic disorder, comorbid health problems and specific personal health, health and family characteristics after testing negative for acute cardiac events. The poster examines the differences among the women who participated in the study.

Methods: This study was a survey design of a convenience sample of patients discharged from the emergency service with negative cardiac testing and no referral. After completion of their cardiac evaluation, potential subjects were asked by the Emergency Room personnel if they would consider a structured diagnostic interview with one of the investigators. If the subject agreed, informed consent was obtained and the interview was conducted immediately. Subjects diagnosed and in need of treatment were referred immediately. Data analysis included descriptive and inferential statistics: between group comparisons were analyzed using chi-square and independent t-tests, relative risk was determined for diagnoses by race and gender.

Significant Results: Total N = 40, WF = 13; BF = 14. Ninety percent of total sample met DSM IV criteria for Panic Disorder, and 35 of 36 subjects had at least one comorbid diagnosis. Of the female subjects meeting the criteria for Panic Disorder, White females had a 42% greater incidence of comorbid agoraphobia, a 100% greater incidence of comorbid alcohol abuse, a 41% greater incidence of PTSD. Black women had 49% higher incidence of Isolated Sleep Paralysis.

Conclusions: The prevalence and severity of Panic Disorder remains underestimated and under diagnosed in black populations served in Emergency room settings. There are few differences between black and white women in the syndrome itself, but cultural, demographic and psychosocial factors in this sample may support racial differences in comorbidity. The social and economic cost of diagnosing anxiety disorders in a tertiary care center supports further research aimed at developing cost effective, evidence based models for early detection and intervention in the community. This study supports this is true in the black community, before symptoms become so debilitating that scarce and costly healthcare resources are utilized ineffectively, and the patient remains undiagnosed, untreated and continues to suffer.

Source of Funding: None

Session I – 57

Polypharmacy and Comorbidity in Childhood and Adolescent ADHD

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Background: To examine the prescribing pattern regarding polypharmacy in childhood and adolescent ADHD upon discharge from inpatient hospitalization.

Method: A total of 1499 patients were selected with a primary diagnosis of ADHD or MDD upon discharge from hospital during January 1, 2000 to April 30, 2002. Data was analyzed to determine rationale use of polypharmacy in patients with more than one primary diagnosis.

Results: Out of the total of 1499 samples, 436 had a primary diagnosis of MDD and 65 had comorbid ADHD as a subsequent diagnosis. 295 had a primary diagnosis of ADHD and 16 had comorbid MDD as a subsequent diagnosis. A total of 81 has diagnostically determined basis to be prescribed more than one psychotropic, however, the actual number of patients on polypharmacy were 324.

Conclusion: The obtained data displays a huge discrepancy in prescribing pattern of multiple psychotropic medication in children and adolescent in absence of clinical diagnosis mandating polypharmacy.

Source of Funding: None.

Session I – 58

Medicaid Eligibility Categories and Psychotropic Medication Prevalence Among Youths

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Background: Psychotropic medication trends for Medicaid-eligible youths revealed substantive increases during the 1990s (Zito et al, 2003). These one-year prevalence findings utilized Medicaid data from 2 states in the US, but the data analyses were not disaggregated by eligibility category [e.g., foster care, supplemental security income (SSI) status, and low income status (TANF)]. Prominent differences in prevalence according to Medicaid eligibility categories were reported in a one county assessment in 1996 (dosReis et al. 2001). The present study adds an additional eligibility category, the state Children's Health Insurance Program (s-CHIP)—which represents Medicaid eligible youths from low income employed families—and thus analyzes data from all 4 major eligiblity categories.

Method: Computerized Medicaid data from a mid-Atlantic state were analyzed for patterns of psychotropic medication utilization by youths (<20 years old) for the years 1990, 1995 and 2000. Trend data for the total population (ranging from 183,397 in 1990 to 308,538 in 2000) were analyzed according to total and age-, gender- and race-specific prevalence. The data were also analyzed by eligibility category (foster care, SSI, TANF and s-CHIP) for the year 2000. The annual prevalence per 100 eligible youths was calculated for 'any' psychotropic medication and for leading psychotropic classes and subclasses.

Results: The major findings are: 1) In 2000, the annual prevalence for 'any' psychotropic medication for youths was 34% for SSI, 25% for foster care, 7% for TANF and 5% for s-CHIP. 2) Neuroleptics were far more frequently prescribed to youths in foster care (7%) and SSI (12%) than for youths in either income eligibility category (0 .5% TANF and s-CHIP 0.9%). 3) Prevalence ratios showed the following increases from 1990 to 2000: 3-fold for methylphenidate, 30-fold for amphetamines, and 44-fold for alpha-agonists. 4) Racial disparities across the decade showed a 2-3-fold greater use among White youths compared with Black youths. 5) The 10-year prevalence rate ratio for 'any' psychotropic medication increased linearly with age.

Conclusion: Disaggregating Medicaid data by eligibility category reveals large differences in psychotropic prevalence that reflect differences in clinical and social impairment. Psychotropic prevalence rates for Medicaid-insured youths have continued to rise since 1987.

Source of Funding: University of Maryland DRIF funds

Session I – 59

Hyperprolactinemia in Children and Adolescents Treated with Atypical Antipsychotics

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Background: Although risperidone has been linked to hyperprolactinemia more frequently than other atypical antipsychotics in the adult population, this has not been studied in children and adolescents. Few studies showed moderate increase in prolactin levels by risperidone.
We hypothesized that risperidone would cause hyperprolactinemia more frequently than olanzapine and quetiapine based on its relatively strong D2 blocking capacity.

Methods: Subjects prescribed an atypical antipsychotic medication were recruited from consecutive admissions to our child and adolescent psychiatry inpatients units and outpatient department. Fasting prolactin levels were drawn at baseline and after 12 weeks of treatment. If the antipsychotic was to be discontinued for any reason, end point prolactin levels were drawn at that time.
An analysis of covariance was conducted with endpoint prolactin levels as the dependent measure, baseline prolactin levels as a covariate and drug treatment group, as a fixed effect.

Results: Baseline and end point assessments were completed on 39 patients (18 females, 21 males, mean age= 13.44, SD= 2.66, range, 5-18 years). Twenty- one were on risperidone, 12 on olanzapine and 6 on quetiapine. The mean duration of treatment was 11.78 weeks, SD= 0.94, range, 6-15 weeks. Hyperprolactinemia (defined as > 25.4 ng/ml for children in our laboratory) was present in 53.8% of our overall sample. Seventy one percent of risperidone treated patients had abnormally elevated prolactin levels compared to 29% of those treated with olanzapine or quetiapine. (chi-square p=.017) The risperidone treated group had a significantly higher mean endpoint prolactin levels (46.08 ng/ml, SD=30.2) compared to olanzapine or quetiapine treated group (22.86 ng/ml, SD=16.8; F=6.89, df=1.37, p=0.013).

Conclusion: Hyperprolactinemia was present in more than half of our sample after 12 weeks of treatment with an atypical antipsychotic medication. Risperidone increased prolactin levels in children and adolescents significantly more than olanzapine or quetiapine. This sample is more representative of clinical samples than previous reports in its diversity of diagnoses, and gender and age distribution. The long-term effects of hyperprolactinemia in children and adolescents, including on pubertal maturation and bone density, are unknown.

Source of Funding: Departmental funding.

Session I – 60

Pharmacokinetics of Ziprasidone in Pediatric Versus Adult Subjects

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Objective: To compare the single-dose pharmacokinetics of oral ziprasidone in children and adolescents with that in adults.

Methods: Three groups of 8 pediatric subjects (age range 7 to 16 years) were assigned a dose of ziprasidone on the basis of body weight: Group 1 (>60 kg), 20 mg; Group 2 (31-60 kg), 10 mg; and Group 3 (16-30 kg), 5 mg. Dose in mg/kg was calculated for each group. Pharmacokinetic values for the groups were compared with each other and with data from a single-dose study of 40 mg in 10 adults.

Results: Mean doses adjusted for body weight for Groups 2 and 3 were 19% and 38% lower than for Group 1; mean values were correspondingly lower for $AUC_{0-\infty}$ and C_{max}. T_{max}, $T_{1/2}$, and oral clearance (Cl/F) were similar for the three groups, and these values for the groups were comparable to values in adults. Linear regression analysis for $AUC_{0-\infty}$ vs dose adjusted for weight indicated pharmacokinetic linearity between children and adolescents and adults.

Conclusions: Similarities in T_{max}, $T_{1/2}$, and Cl/F observed in adults and children and adolescents indicate that the pharmacokinetics of oral ziprasidone is comparable in these populations. Pharmacokinetics is linear in pediatric subjects, and appears also to be so in adults.

Source of Funding: Pfizer, Inc.

Session I – 61

Ziprasidone Treatment in Adolescents with Autism: A Pilot Study

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Background: Patients with autism may benefit from treatment with antipsychotics but can have drug-associated weight gain. Ziprasidone is purportedly weight neutral, a potential health advantage, but may prolong the QTc interval. This pilot study investigated the safety and efficacy of ziprasidone in adolescents with autism.

Methods: The study was a 6-week open-label trial that used an individual titration strategy. Eight adolescents diagnosed with autism (DSM-IV) enrolled in the study; one never received drug. All were males (females were eligible) with a mean age of 14.4 ± 1.7 years. Exclusion criteria included major medical problems, concomitant psychotropics, and baseline QTc > 425 msec. Efficacy measures included the CGI. Safety was assessed systematically. Laboratory tests and ECGs were completed at baseline and at end of trial.

Results: Mean ziprasidone dosage was 91.4 ± 47 mg/day. On the CGI, one subject was rated as very much improved, 3 as much improved, 2 as minimally improved, and one as not changed. The mean change in the BMI was 0.06 ± 1.0 and in the QTc was 19.2 ± 30.6 msec. Adverse events included drowsiness, decreased appetite, and EPS.

Conclusion: Findings suggest ziprasidone is safe and effective in this population, but further study is needed.

Source of Funding: This study was supported in part by Pfizer (Investigator-initiated, RP Malone).

Session I – 62

Multicenter Study of Adolescents with Schizophrenia: Efficacy and Safety of Olanzapine

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Objective: To present first results from a study of olanzapine in the treatment of adolescent patients with schizophrenia.

Background: The majority of psychotropic compounds do not have regulatory approval for use in adolescents. Efficacy and safety data on these drugs, including olanzapine, are scarce for this age group.

Methods: This is an open-label multicenter trial of olanzapine (5-20mg/day) in adolescents (12-21 years old) with DSM-IV diagnosis of schizophrenia. We used BPRS (response criterion at Week 6: $\geq$ 30% in BPRS reduction), CGI, Subjective Well-being (SWN), and QoL scales to assess the efficacy of olanzapine. Safety was assessed based on Simpson-Angus scores, spontaneous adverse events (AEs), weight, and laboratory analytes. Interim safety analyses (up to Week 6) were performed once 50 patients had completed 6 weeks of olanzapine therapy (or dropped out).

Results: In total, 100 patients entered the study, 80 reached week 6, and 35 of them completed the 6-month observation period. The response rate at Week 6 was 60% (N=60/100). Interim safety analyses were performed on 51 patients; the results from these analyses were as the following: Mean length of olanzapine treatment (mean maximum dose=16.5mg/day) was 95 days. Two patients had serious AEs (rehospitalization). The most common treatment-emergent AEs were weight gain (N=11; 22%); tremor (N=9; 18%); headache (N=8; 16%); akathisia (N=6; 12%); increases of hepatic enzymes (N=10; 20%), prolactin (N=7; 14%), and creatine kinase (N=6; 12%); and leukopenia (N=2; 4%) and neutropenia (N=1; 2%). Minimal changes (baseline-to-endpoint) in blood pressure, heart rate, and body temperature were observed. Mean weight gain was 4.4kg; BMI increase, 1.5 (inversely related to baseline BMI). Mean change in Simpson-Angus score was -0.6.

Final results both on efficacy and safety will be presented on the full data set.

Conclusions: Data from this ICH-compliant trial revealed the following: feasibility of conducting psychopharmacology trials in adolescents; demonstrated efficacy of Olanzapine; interim safety results consistent with those seen in adults. The final results from this sample will offer valuable information for antipsychotic treatment of adolescent patients with schizophrenia.

Source of Funding: Lilly Deutschland GmbH, Bad Homburg, Germany

Session I – 63

Atomoxetine in the Treatment of Young Children with ADHD

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Background: Atomoxetine is a selective norepinephrine reuptake inhibitor recently approved by the FDA for the treatment of ADHD in individuals 6 years of age and older. Because ADHD is a disorder with an early age of onset and one that is often treated with pharmacotherapy, many young children will likely be treated with this novel medication.

Methods: Throughout the past 4 years over 3,500 children and adolescents have been treated with atomoxetine in double-blind and open-label clinical trials. As of this date, 323 6- and 7-year old children have been entered into atomoxetine clinical trials, 126 in double-blind studies and 197 in open-label studies. Efficacy and safety data for this young population has been summarized from these studies.

Results: In the placebo-controlled trials, subjects receiving atomoxetine did significantly better on the Hyperactive/Impulsive Subscale ($p<.001$), Inattentive Subscale ($p=.002$), and ADHD Total Subscale of the ADHD-IV Rating Scale ($p=.001$), as well as the CGI-ADHD-S ($p=.037$). In the open-label trials subjects receiving atomoxetine demonstrated significant within group change ($p<.001$) for all 3 of the ADHD-IV scales and the CGI-ADHD-S scale.

Atomoxetine was well tolerated, with only 3 discontinuing for adverse events from double blind trials (2 of 80 receiving atomoxetine and 1 of 46 receiving placebo), and 8 (of 197) from open-label trials. The treatment emergent adverse events reported in this population were similar but occurred with a greater frequency than adverse events reported in the trials for the entire pediatric sample.

Conclusion: The data reviewed support the use of atomoxetine in young children as a safe and effective treatment for ADHD. Additional studies, particularly assessing the long-term safety of this medication, are indicated.

Source of Funding: The clinical trials reviewed were funded by Eli Lilly and Company.

Session I – 64

Paroxetine Improves School Performance Measures in Children and Adolescents with Social Anxiety Disorder: A Retrospective Analysis

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Background: Paroxetine has been shown to be effective in reducing social anxiety disorder (SAD) symptoms in pediatric patients, based on change from baseline in the Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA) total score. SAD in children and adolescents has been associated with impaired school performance since many school related situations (answering questions in class, speaking to teachers or performing in front of others) produce extreme anxiety and fear of scrutiny, which is the essential feature of SAD. In this analysis we looked specifically at those LSAS-CA items which pertain to school performance.

Objective: The aim of this retrospective analysis was to investigate whether children and adolescents with SAD randomized to paroxetine improved in LSAS-CA school performance measures compared to placebo.

Method: The data were derived post-hoc from a previously reported 16-week, multicenter, double-blind, placebo-controlled study of the efficacy and safety of paroxetine (10-50mg/day) in children and adolescents with SAD. Only the results from eight "school performance-related" items of the LSAS-CA were included in these analyses.

Results: The Intent-to-Treat (ITT) population consisted of 319 children (8-11 years, n=91) and adolescents (12-17 years, n=228) randomized to paroxetine (n=163) or placebo (n=156). The adjusted mean difference between paroxetine and placebo in change from baseline in the subtotal eight LSAS-CA school performance items at Week 16 LOCF was -8.12 points in favor of paroxetine (95% CI: [-10.30, -5.94], $p < 0.001$). Similar results were seen for the child and adolescent age subgroups alone.

Conclusion: Treatment with paroxetine may improve school performance in children and adolescents with SAD.

Source of Funding: Supported by funding from GlaxoSmithKline

Session I – 65

Venlafaxine XR and Paroxetine in the Short-Term Treatment of Panic Disorder

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Objective: To compare the efficacy and safety of venlafaxine extended release (XR) and paroxetine to placebo in the short-term treatment of panic disorder.

Methods: In this multicenter study, 664 adult outpatients with DSM-IV panic disorder (with or without agoraphobia) were randomly assigned to receive 1 of 2 fixed doses of venlafaxine XR (75 mg/day or 150 mg/day), paroxetine (40 mg/day), or placebo for up to 12 weeks. The primary efficacy measure was the proportion of panic-free patients (PAAS scale). Two key secondary measures were the PDSS and response rate (CGI-I≤ 2). Remission was defined as panic free and CGI-I = 1.

Results: Venlafaxine XR and paroxetine-treated patients demonstrated significantly greater improvement on all efficacy measures than placebo-treated patients. No significant differences between venlafaxine XR and paroxetine were observed. At the primary endpoint, the percentage of panic-free patients was 54.1%, 61.4%, 60.0%, and 34.4% for venlafaxine XR 75 mg, venlafaxine XR 150 mg, paroxetine, and placebo, respectively (ITT, final on therapy evaluation, $P<0.001$ for all active treatments vs placebo). There were significantly greater reductions in the total score on the PDSS with venlafaxine XR 75 mg (-9.31), 150 mg (-9.63), and paroxetine (-9.55) than placebo (-6.8) (P value for all active treatments <0.001 vs placebo). In addition, response rates were significantly higher with all active treatments vs placebo (venlafaxine XR 75 mg 76.6%, venlafaxine XR 150mg 79.2%, paroxetine 80.6%, placebo 55.8%: P value for all active treatments <0.001 vs placebo) A significantly greater percentage of patients receiving venlafaxine XR 75 mg (44.6%), venlafaxine XR 150 mg (46.8%), and paroxetine (45.9%) achieved remission compared to patients receiving placebo (26.6%; $P = 0.001$ vs venlafaxine XR 75mg, $P < 0.001$ vs venlafaxine XR 150 mg and paroxetine). The incidence and severity of adverse events were generally comparable with venlafaxine XR treatment and paroxetine treatment.

Conclusion: The results of this study suggest that venlafaxine XR is safe, effective, and well tolerated in the short-term treatment of panic disorder.

Source of Funding: Wyeth Research

Session I – 66

Physiological Symptoms in Panic and Social Anxiety Disorders: Improvement with Venlafaxine XR, Paroxetine and Placebo

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Objective: To compare venlafaxine extended release (VEN XR), paroxetine, or placebo in alleviation of patient-reported physiological symptoms in panic disorder and social anxiety disorder.

Methods: Data were pooled from 2 randomized, double-blind, placebo-controlled studies of VEN XR (75 mg, 150 mg, or flexible dosages), one of which also included a paroxetine control group, during 10-12 weeks of treatment of patients with DSM-IV panic disorder (N=958). Improvement with treatment – at final observation-on-therapy carried forward – on the physical health/activities and nine other sub-scales of the patient-reported Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) was evaluated. Data were separately pooled from 4 randomized, double-blind, placebo-controlled studies (2 of which were also paroxetine-controlled) of flexible-dose VEN XR during 10-week treatment of patients with DSM-IV social anxiety disorder (N=1372). Treatment-related improvement, at the final observation-on-therapy, on the physiological arousal sub-scale (blushing, sweating, palpitations, trembling) of the patient-reported Social Phobia Inventory (SPIN) and on the total SPIN score was examined. The association with clinician-assessed primary efficacy measures was also evaluated for each condition.

Results: In panic disorder, VEN XR was associated with significantly greater improvement, relative to placebo, on the physical health/activities sub-scale ($P<0.0001$) and on 8 of 9 other sub-scales of the Q-LES-Q. Paroxetine was associated with significantly greater improvement, relative to placebo, on the physical health/activities sub-scale ($P=0.0004$) and on 5 of the 9 other sub-scales of the Q-LES-Q. In social anxiety disorder, both VEN XR and paroxetine were associated with significantly greater improvement, relative to placebo, on the physiological arousal sub-scale ($P<0.0001$ each) and the total SPIN score ($P<0.0001$ each).

Conclusions: Physical and somatic complaints are a neglected but important aspect of both panic disorder[1] and social anxiety disorder[2]. VEN XR, as also paroxetine, was associated with significant improvement not only in clinician-measured efficacy but also in alleviating self-reported physical complaints in both these anxiety disorders.

Source of Funding: Wyeth Research

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Session I – 67

The Impact of 9/11 Disaster on Generalized Anxiety Disorder Research Population

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Objective: Differences in baseline characteristics and treatment outcome between generalized anxiety disorder (GAD) patients participating in clinical trial before and after September 11, 2001 were examined.

Methods: DSM-IV GAD subjects in a 10-week placebo-controlled sertraline treatment trial were classified post hoc into those completing prior to 9/11 (n=237) and those entering after 9/11 (n=75). Baseline characteristics and outcome variables were compared using standard statistical analyses.

Results: Although no differences in age, education, ethnicity, gender, GAD duration, and completion rates were noted, significantly higher proportion after 9/11 were divorced (26.7% vs.13.5%) and had history of psychiatric disorders (34.6% vs. 23.5%), particularly major depression (24 % vs.15.8%). Subjects after 9/11 had significantly higher baseline anxiety and depression (MADRS 12.3vs 13.6; HAD 21.1vs 23.0), and lower quality of life scores (Q-LES-Q 64.1vs 61.3). Change in HAM-A total scores was significantly lower after 9/11 due primarily to increased placebo effect. Finally, prior to 9/11, subjects experienced more rapid decline in anxiety symptoms during the first week of treatment (30% vs. 16% with $\geq$ 20% reduction in HAM-A scores).

Conclusion: The effects of a major national trauma are far-reaching and should be considered when examining clinical research studies conducted shortly following the 9/11 disaster.

Funding Source: Investigator Initiated Grant to Dr. Brawman-Mintzer from
Pfizer Pharmaceutical Co.

Session I – 68

The SGRI Tiagabine for the Treatment of Generalized Anxiety Disorder

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Objective: Gamma-aminobutyric acid (GABA), the main CNS inhibitory neurotransmitter, is known to be involved in the pathophysiology of anxiety and sleep. The selective GABA reuptake inhibitor (SGRI) tiagabine enhances normal GABA tone and has been shown to reduce anxiety and improve sleep quality in preliminary reports. This study aimed to evaluate the benefits of tiagabine in patients with generalized anxiety disorder (GAD).

Method: Patients with DSM-IV GAD received open-label tiagabine for 8 weeks in a fixed-flexible dose design. Patients received tiagabine 4 mg/day (2 mg bid) during week 1, with doses increased for optimum response by 2 mg every 3 days to a maximum of 16 mg/day (bid dosing). Assessments included the Hamilton Rating Scale for Anxiety (HAM-A) and Pittsburgh Sleep Quality Index (PSQI). Last-observation-carried-forward methodology was employed.

Results: Eighteen patients have entered the 8-week study to date. Mean tiagabine dose was approximately 10 mg/day (range: 4-16 mg/day). Improvements in anxiety symptoms and sleep quality were observed early, usually within the first two weeks of treatment. The mean HAM-A total score ± SEM decreased significantly from 28.1 ± 1.4 at baseline to 16.4 ± 1.8 at endpoint (P<0.001) with significant decrease evident at each observation after one week of treatment. The mean psychic and somatic anxiety subscale scores of the HAM-A were both reduced significantly from 14.1 ± 0.57 and 14.0 ± 0.94, respectively, at baseline to 9.1 ± 0.93 and 7.3 ± 0.98, respectively, at endpoint (both P<0.001). For sleep quality, the mean PSQI score also decreased significantly from 10.6±0.98 at baseline to 7.8 ± 0.85 at endpoint (P<0.05). Among the 18 patients exposed to tiagabine, the most commonly reported adverse events were asthenia, somnolence, and inability to concentrate. Four patients discontinued due to adverse events. Full dataset from the ongoing study will be presented.

Conclusion: The SGRI tiagabine may improve both somatic and psychic anxiety symptoms and sleep quality in patients with GAD. These results encourage further systematic study of tiagabine in the treatment of anxiety disorders, and particularly in those with comorbid sleep problems.

Source of Funding: Supported by Cephalon, Inc.

Session I – 69

Pregabalin Significantly Improves Patient Reported Work Productivity in a Placebo-Controlled, Double-Blind Trial Among Patients with Generalized Anxiety Disorder

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Objective: Previous reports documented the efficacy of pregabalin in the treatment of patients with Generalized Anxiety Disorder (GAD). This report presents the results of analysis of the Endicott Work Productivity Scale (EWPS), a secondary endpoint.

Methods: After completing a 1 week screening phase, 455 patients with generalized anxiety disorder were randomized to 4 weeks of double blind treatment with pregabalin 300 mg/day, pregabalin 450 mg/day, pregabalin 600 mg/day, alprazolam 1.5 mg/day, or placebo, all dosed TID. Patient-reported work productivity was assessed at baseline and week 4 using the EWPS, a 25 item, self-administered questionnaire. Patients were required to have worked the week prior to completing the EWPS.

Results: Patients treated with pregabalin 600 mg/day reported a significantly greater improvement in self-reported work productivity scores than patients receiving either placebo ($p=0.02$) or alprazolam ($p=0.02$). Patients treated with other doses of pregabalin also reported improvements in work productivity, though these improvements were not significantly different from either placebo or alprazolam. Patients treated with alprazolam reported EWPS change scores that were not significantly different from placebo ($p=0.99$).

Conclusions: Patients treated with pregabalin 600 mg/day reported improved work productivity compared to patients treated with placebo or alprazolam 1.5 mg/day.

Source of Fuding: Pfizer, Inc.

Session I – 70

Artofisopam: A Nonsedating "Antistress" Agent with No Significant Impairment of Cognition

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Background: Tofisopam is a 2,3-benzodiazepine that has been marketed in Europe, Asia, and North Africa for many years. It has demonstrated efficacy in a wide range of therapeutic applications, including anxiety, functional gastrointestinal (GI) disorders, somatoform disorders, perimenopausal symptoms, hypertension, depression, and disorders of autonomic function. We separated racemic tofisopam, a chiral compound, into its R- and S-enantiomers.

Methods: Artofisopam[USAN], the R-enantiomer of tofisopam, was tested in a series of animal behavioral models, including the elevated plus-maze, the water-immersion stress test, the charcoal meal test, and the glass bead expulsion test. Artofisopam was also tested in two randomized, double-blind, placebo-controlled studies in healthy volunteers. In the first clinical trial, single doses of 50, 100, 200, 300, and 400 mg artofisopam or placebo were administered to a total of 72 volunteers. In the second trial, dosages of 100, 150, and 200 mg TID and 400 and 600 mg BID artofisopam or placebo were administered for 7 days to 44 volunteers. Safety and pharmacokinetics were assessed in both studies, and tests of cognitive function were conducted in the multiple-dose trial, including simple reaction time, word recall, attention, and executive function. Self-rated alertness was also evaluated by means of a visual analog scale.

Results: In contrast with classical, 1,4-benzodiazepines such as diazepam, artofisopam showed no activity in the elevated plus-maze. However, in the water-immersion stress test, treatment with artofisopam was associated with a clear, consistent, and dose-dependent decrease in the occurrence of stress-induced ulcers. Although it had little effect on gastric emptying or upper GI motility in the charcoal meal test, artofisopam was associated with a dose-dependent decrease in induced contractile activity in the glass bead expulsion test, an animal model of IBS. Safety data from the Phase I studies indicate that single doses up to 400 mg artofisopam and multiple doses up to 600 mg BID were well tolerated. Pharmacokinetic data indicate that artofisopam reached peak plasma concentrations approximately 1 hour after oral dosing regardless of dose, with an harmonic mean half-life ranging from 6.2 to 11.0 hours. Results from tests of cognitive function indicate that artofisopam has no significant impact on cognitive or psychomotor performance. There were no significant changes in self-rated alertness or evidence for increased sedation relative to placebo.

Conclusion: Artofisopam was not active in the elevated plus maze, but was active in the water-immersion stress test and the glass bead expulsion test. This suggests that artofisopam may have an anxiolytic or "antistress" profile distinct from that of the 1,4-benzodiazepines. These findings, accompanied by a low incidence of sedation and lack of impact on cognitive performance, suggest that artofisopam may be of value in the treatment of conditions related to stress, including anxiety and such functional GI disorders as ulcers and IBS.

Source of Funding: Research supported by Vela Pharmaceuticals Inc.

Session I – 71

Treatment of Anxiety Disorders in Elderly Subjects: A Controlled Study with Citalopram

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Currently there exist no published controlled studies of antidepressants in late life anxiety disorders. This study's aim is to determine efficacy of citalopram in acute treatment of elderly subjects with anxiety disorders. The study is ongoing; to date, we have recruited 23 subjects, aged 60 and older, with a DSM-IV anxiety disorder and a Hamilton Anxiety Scale (Ham-A) score 17 or greater, and without co-existing psychiatric disorders, to a flexible 8-16 week randomized controlled trial. Most subjects were recruited to our specialty mental health research center via advertisements or referrals. After a psychotropic medication-free period (other than stable dose of lorazepam), were randomized to citalopram 10-40mg/day in flexible dosing, or placebo. The sample had a mean (SD) age of 69.6 (5.9) years; 74% (17/23) were female. Mean baseline Ham-A was 20.9. Most subjects (64%) had generalized anxiety disorder as their primary diagnosis.

Of the 23 recruited subjects, 5 are currently in active treatment and 4 dropped out prematurely (3 in the citalopram group and 1 in the placebo group). For the 14 completers, the primary and secondary outcomes were change in Ham-A and CGI scores, respectively. At week 8, citalopram-treated subjects had a mean 12.3 drop in Ham-A, compared to 5.1 drop in placebo-treated subjects ($t = -2.9$, $p = 0.014$). At end of acute, 5/7 citalopram-treated subjects and 2/7 placebo-treated subjects had CGI scores in the much to very much improved range, a non-significant difference.

To our knowledge, this is the first controlled study to test the efficacy of a serotonin reuptake inhibitor in the management of elderly persons with anxiety disorders. While this interim analysis preliminarily demonstrates efficacy, the effectiveness of such medications for geriatric anxiety disorders should be demonstrated in a larger and more generalizable sample.

Source of Funding: This protocol is supported by an investigator-initiated grant from Forest Pharmaceuticals, as well as funding from NIMH grants K23 MH64196 and P30 MH52247.

Session I – 72

Treatment of Panic Disorder with Venlafaxine XR

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Objective: To determine the efficacy and safety of venlafaxine extended release (XR) in the short-term treatment of panic disorder.

Methods: In this multicenter, randomized, placebo-controlled, parallel-group study, 361 adult outpatients with DSM-IV panic disorder (with or without agoraphobia) were randomly assigned to receive either a flexible dose of venlafaxine XR (75 to 225 mg/day) or placebo for up to 10 weeks. The primary efficacy measure was the proportion of patients free from panic attacks (PAAS scale). Secondary efficacy measures included the proportions of responders (Clinical Global Impression-Improvement [CGI-I] = 1 or 2]) and remitters (panic-free and CGI-I=1), as well as the reduction in panic attack frequency.

Results: At the primary endpoint, 55% of patients receiving venlafaxine XR and 52.4% of patients receiving placebo were free from panic attacks (intent-to-treat population; final on therapy evaluation). The proportion of responders and remitters were greater in the venlafaxine XR treatment group than in the placebo group (response: 68.1% vs 55.4%, $P<0.05$; remission: 35.6% vs 24.4%; $P<0.05$). In addition, venlafaxine XR was superior to placebo in reducing panic attack frequency (median change from baseline of – 5.0 vs –3.7, respectively, $P<0.05$). The incidence and severity of adverse events associated with venlafaxine XR treatment were comparable with those observed in patients with depression and generalized anxiety disorder who received venlafaxine XR.

Conclusions: The results of this study suggest that venlafaxine XR is a safe, effective, and well tolerated in the short-term treatment of panic disorder.

Source of Funding: Wyeth Research

Session I – 73

A Placebo-Controlled Trial of Pimozide Augmentation of Fluoxetine in Body Dysmorphic Disorder

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Background: Although BDD has been shown in open-label trials and two controlled studies to respond to SRIs, a majority of patients do not respond or respond only partially. However, no placebo-controlled SRI augmentation studies have been done. Furthermore, although 40%-50% of BDD patients are delusional, no open or controlled studies of antipsychotics have been done. Pimozide was selected as an SRI augmentation agent because antipsychotics have been widely used in BDD and because pimozide in particular has been proposed to be uniquely effective for somatic delusions and BDD. In addition, pimozide is an efficacious SRI augmentor for OCD, which has many similarities to BDD.

Methods: 36 patients with DSM-IV BDD or its delusional variant (delusional disorder, somatic type) were enrolled and 28 were randomized into an 8-week double-blind parallel group study of pimozide versus placebo augmentation of fluoxetine. All subjects received fluoxetine for at least 12 weeks before randomization to pimozide or placebo, with 80 mg/day attained if tolerated. Entry criteria included nonresponse to fluoxetine and the absence of excellent or good insight regarding the perceived appearance "defect." Patients continued treatment with fluoxetine and were randomized to 8 weeks of double-blind augmentation with pimozide or placebo. They were assessed at regular intervals with the BDD-YBOCS (a reliable and valid measure of BDD severity), the Brown Assessment of Beliefs Scale (a reliable and valid measure of delusionality [insight]), and other measures.

Results: Controlling for baseline group differences in BDD severity, pimozide (mean dose=1.7 ± 1.0 mg/day) was not significantly more effective than placebo as a fluoxetine augmentor for BDD symptoms ($F(1,25)=.97$, $p=.34$). The response rate to pimozide was 18.2% (n=2) and to placebo was 17.6% (n=3) (chi square=.001, df=1, $p=.97$). There was no significant effect of baseline delusionality on BDD severity at endpoint. Controlling for baseline delusionality, degree of delusionality did not decrease significantly more with pimozide than placebo treatment.

Conclusion: Pimozide was not more effective than placebo as a fluoxetine augmentation agent, even in delusional patients. In addition, pimozide was not superior to placebo in improving delusionality. Although power was limited, these results are not promising. Additional SRI augmentation studies are needed.

Source of Funding: NARSAD

Session I – 74

Quetiapine Augmentation in Obsessive-Compulsive Disorder Resistant to Serotonin Reuptake Inhibitors: An Open-Label Study

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Background: Many patients with obsessive-compulsive disorder (OCD) are treatment-resistant to serotonin reuptake inhibitors (SRIs). In such cases, evidence supports augmentation of the SRI with an atypical neuroleptic. We describe an open-label study of quetiapine augmentation in OCD treatment-resistant to SRIs. We also review current literature on augmentation strategies with atypical neuroleptics in SRI-resistant OCD.

Methods: In an eight-week trial, sixteen adults with a primary DSM-IV diagnosis of OCD treatment-resistant to at least one adequate SRI trial received augmentation of their current medication regimen with quetiapine. Behavioral ratings including Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression – Severity (CGI-S), and Clinical Global Impression – Improvement (CGI-I) were obtained.

Results: Fourteen subjects (87.5%) completed the trial; two withdrew due to adverse effects. The subjects' mean Y-BOCS score was 27.7±7.0 (range, 13 [obsessions only] - 39) at baseline and 23.3±8.4 (range, 6-36) at endpoint. The mean percent change in Y-BOCS was a decrease of 16.3%±22.7. The responder rate, defined as ≥ 25% decrease in Y-BOCS score, was 31.3% (5/16). All participants experienced at least one adverse event, but most were mild. The most common adverse effects were sedation (11/16) and fatigue (9/16).

Conclusion: Though SRIs are the most effective treatment available for OCD, quetiapine augmentation may benefit treatment-resistant OCD. Despite the history of treatment resistance in our subjects, nearly one-third responded. Our responder rate of 31.3% falls within the range of other augmentation trials (30-100%). However, we cannot confidently compare our responder rate to that observed in other studies primarily because of potential differences in the nature of the study subject samples and study designs. An additional problem in attempting comparisons is the large confidence interval that surrounds responder rates observed in studies with small sample sizes. Large-scale, double-blind, placebo-controlled trials are needed to discover predictors of efficacy and safety. Additionally, head-to-head comparisons of quetiapine with other atypical neuroleptic agents are needed to establish their comparative safety and efficacy.

Source of Funding: Research supported by a grant from Astra-Zeneca Pharmaceuticals

Session I – 75

Paroxetine Treatment of Pathological Gambling: A Multi-Center Randomized Controlled Trial

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Background: Previous studies have suggested the efficacy of serotonergic agents in the treatment of pathological gambling. The purpose of the present study was to determine if treatment with paroxetine in a larger sample of subjects with pathological gambling, recruited from diverse geographical sites, would effectively and safely diminish the frequency and severity of gambling symptoms.

Method: Subjects were recruited for a sixteen-week, double-blind, placebo-controlled trial conducted at five outpatient academic research centers in 2 countries (United States and Spain). Seventy-six outpatients (mean age, 45.4 ± 10.6 years; thirty women [39.5%]) with pathological gambling were randomized to acute treatment with paroxetine in flexible daily dosages of 10 to 60 mg/d (n = 36) or placebo (n = 40). The primary outcome measure assessing change in clinical status was the Clinical Global Impressions scale (PG-CGI). Secondary measures included the Yale-Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS) and the Gambling Symptom Assessment Scale (G-SAS).

Results: Both the paroxetine- and the placebo-treated groups demonstrated comparable improvement at 16 weeks (59% response rate in the paroxetine group, 49% rate in the placebo group)(chi square = .737; df = 1; p = .390). As determined by scores on the PG-YBOCS, G-SAS and PG-CGI, paroxetine was superior to placebo during the first four weeks of treatment.

Conclusions: High rates of symptom improvement were observed in pathological gamblers receiving either paroxetine or placebo after 16 weeks. Paroxetine may hasten symptom resolution in the treatment of pathological gambling.

Source of Funding: GlaxoSmithKline Pharmaceuticals

Session I – 76

Overt Aggression and Psychotic Symptoms in Patients with Schizophrenia Treated with Clozapine, Olanzapine, Risperidone, or Haloperidol

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Objective: Published studies of antiaggressive treatments are largely uncontrolled and use indirect measures of aggression. We present the effects of four antipsychotics on incidents of overt aggression in a controlled study.

Methods: The subjects were 157 treatment-resistant inpatients diagnosed with chronic schizophrenia or schizoaffective disorder. They were randomly assigned to treatment with clozapine, olanzapine, risperidone, or haloperidol in a 14-week double-blind trial. Incidents of overt physical aggression were recorded and their severity scored. A standard measure of clinical antipsychotic efficacy (PANSS) was administered.

Results: Atypical antipsychotics showed an overall superiority over haloperidol, particularly after the first 24 days of the study when dose escalation of clozapine was completed. Once an adequate therapeutic dose of clozapine was reached, it was superior to haloperidol in reducing the number and severity of aggressive incidents. Patients exhibiting persistent aggressive behavior showed less improvement of psychotic symptoms than the other patients. There was an interaction between aggressiveness, medication type, and antipsychotic response: risperidone and olanzapine showed better antipsychotic efficacy in patients exhibiting less aggressive behavior; the opposite was true for clozapine.

Conclusions: Clozapine appears to have superior antiaggressive effects in treatment-resistant patients; this superiority develops after the patient has been exposed to an adequate dose regimen. The interaction between medication, aggressiveness, and treatment response suggests that the information about the level of aggressive behavior is critically important for a choice of treatment: clozapine should be the first-line atypical antipsychotic in patients with schizophrenia showing persistent aggressive behavior.

Source of Funding: NIMH grant (R10 MH53550)

Session I – 77

Intermittent Explosive Disorder: DSM-IV Vs. Modified Criteria Usefulness in Treatment Studies of Impulsive Aggression

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Background: Medication studies for impulsive aggression are relatively rare, partly because there is no one diagnosis for most patients with clinically significant aggression; DSM-IV criteria for Intermittent Explosive Disorder (IED) include only patients who commit "serious assault or destruction of property". Recently, Cocarro et al. proposed modified criteria for IED which allow the diagnosis for patients with only verbal aggressiveness, if the aggressiveness is clinically significant, and allow more concomitant diagnoses.

Method: Two medication studies (one a multi-site study) for impulsive aggression included 68 patients at one site. Clinically significant aggressiveness was required for entry into either study, providing an opportunity to determine whether these patients met DSM-IV criteria for IED. Other patient characteristics were evaluated, including concomitant diagnoses, family history, and severity of temper. Other psychiatric problems requiring treatment were exclusionary.

Results: Recruitment was comparable to recruitment for other studies, e.g., for depression, in terms of advertising cost per patient entered.

Of the 68 patients, mean age 40.5 years, only 13 met DSM-IV criteria for IED; 23 may have previously met DSM-IV criteria (i.e., tempers were worse in the past). All patients met the modified criteria. Twenty-six patients had had ADHD, 19 had prior substance abuse, and 21 had prior Major Depression.

Patients lost their temper more than 10 times/week, on average, but physical assault in the prior month was rare (only 8 patients) and not serious. Sixty-six patients slammed doors, etc., and 36 had broken inconsequential items, e.g., a dish, in the prior month, but only 7 had damaged anything of more value. Fifty-four patients had "road rage"; 20 (in the past) had gotten out of a car to argue. Due to temper problems, all had had interpersonal difficulties, 39 had had work difficulties, and 22 had had legal difficulties. Twenty-four had been treated for temper problems. Forty patients had a family history of temper problems.

Conclusion: Patients with clinically significant aggressiveness are not rare. Most do not meet DSM-IV criteria for IED, but do meet modified criteria.

Source of Funding: The two treatment studies which allowed for the collection of this data were funded by Abbott and Novartis.

Session I – 78

Omega Three Fatty-Acids to Decrease Irritable Mood?

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Background: Omega-3 fatty acids (Ω-3FA) are believed to have an effect on irritable mood. Low Ω-3FA levels in red blood cell membranes of depressed patients hint that Ω-3FA may be helpful in treating mood disorders.[1] There have been two published studies that have reported on similar therapeutic effects of Ω-3FA. One placebo-controlled study of 20 patients revealed that ethyl ester of eicosapentaenoic acid (E-EPA) was effective in stabilizing the moods of depressed patients.[2] Another report, a double-blind, placebo controlled study (N=22/19), measured the effect of Ω-3FA docosahexaenoic acid (DHA) on the aggressive tendencies college students. The Ω-3FA DHA group (1.5-1.8g O-FA DHA/day) did not display any increase in aggressive tendencies when external stressors peaked, while the placebo group displayed a significant increase in their aggressive tendencies under similar circumstances.[3] This study suggests that Ω-3FA may help decrease irritable mood and aggressive tendencies. There are no published reports of the effect of Ω-3FA on irritability in patients with mood disorders.

Method: Statistical analysis on 19 subjects who were taking 500mg (60/40 EPA/DHA) - 6000 mg (360/240 EPA/DHA) daily for 4 - 40 weeks. All subjects carried a DSM-IV-TR4 diagnosis of Bipolar Disorder and were visiting a Mood Disorder Clinic regularly through the length of the study. At each visit, subjects reported on the frequency and severity of irritability experienced during the preceding ten days. Frequency was measured by way of percentage of days in which subjects experienced irritability, while severity of that irritability was rated on a Likert scale of 1 - 4 (if present) in the Bipolar Disorder Clinical Monitoring Form (copyright Sachs, G, 1999).

Results: A paired sample t-test revealed a large decrease in the percent of days irritable after Ω-3FA was administered. Before treatment, the mean irritability percentage was 81.05 (SD=23.31) and after treatment the mean irritability percentage dropped to 30.00 (SD=36.67). Despite the small number of patients in the study (n=19), the difference between means was statistically significant ($t(18)4.512$, $p<.001$).

Conclusion: Ω-3FA decrease irritable mood in bipolar patients.

Source of Funding: None

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Session I – 79

Dysphoric Mania: A Controlled Study of the Benefits of Olanzapine Combined with Valproate or Lithium

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Objective: Mixed bipolar episodes carry high suicide risk and the challenge of simultaneously treating dysphoric and manic features. Controlled research is especially limited on treatment of dysphoric features.

Methods: This is a secondary analysis of a 6-week double-blind randomized study of olanzapine 5-20 mg/day or placebo combined with ongoing open valproate or lithium treatment for patients in mixed or manic episodes (N=344). All patients had Young Mania Ratings (YMRS) $\geq$16 despite at least two weeks on lithium or valproate; this analysis focuses on a dysphoric subgroup (baseline Hamilton Depression Rating-HAM-D$\geq$20) contrasted to non-dysphoric patients.

Results: In dysphoric patients (n=85), HAM-D total score improvement was greater in patients receiving olanzapine co-therapy than those taking placebo plus ongoing lithium/valproate ($p<.001$); contributants to this superiority included HAM-D Core Mood cluster ($p=.013$) and the suicide item ($p=.001$). In the non-dysphoric group, HAM-D improvement was greater in olanzapine-treated patients ($p=.002$), although the effect was smaller than in dysphoric patients. Total YMRS improvement was superior on olanzapine co-therapy in both dysphoric and non-dysphoric groups; this effect had similar magnitude in both groups.

Conclusions: In patients with dysphoric mania, addition of olanzapine to ongoing lithium or valproate monotherapy simultaneously improved ratings of depression, mania, and suicidality.

Source of Funding: Eli Lilly and Company

Session I – 80

Mania Remission Rates in a Randomized Controlled Trial of Risperidone

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Background: The purpose of this analysis was to compare remission rates of mania between risperidone and placebo in a randomized controlled trial.

Method: Two hundred ninety (290) adult patients who met DSM-IV criteria for Bipolar I Disorder Manic or Mixed episode were randomized to flexible doses of risperidone (1 mg - 6 mg daily) or placebo for up to 3-weeks. An entry YMRS score of $\geq$ 20 was required at trial screening and baseline. Time to first onset of remission (as defined as a YMRS score of $\leq$ 8) was assessed using Cox proportional hazards. Presence or absence of sustained remission was analyzed using logistic regression. Sustained remission was defined as maintaining a YMRS $\leq$ 8 for the remainder of the trial or until censor.

Results: Forty-one percent (41.7%) of patients on risperidone and 6.2% of patients on placebo achieved remission by the third week. The unadjusted odds of sustained remission for subjects on risperidone was 5.0 (95% CI: 2.8, 9.1; $\chi^2 = 31.4$, $P < 0.0001$). The unadjusted hazard of remission for subjects on risperidone was 3.7 (95% CI: 2.2, 6.2; $\chi^2 = 23.5$, $P < 0.0001$).

Conclusion: Risperidone was superior to placebo in achieving remission of bipolar mania.

Source of Funding: Johnson & Johnson Pharmaceutical Research & Development, LLC

Session I – 81

Quetiapine Adjunctive Therapy for Acute Mania Associated with Bipolar Disorder (SIAM)

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Objective: Evaluate the efficacy and safety of quetiapine as adjunct therapy to mood stabilizer (MS) (lithium [Li] or divalproex [DVP]) in the treatment of acute mania.

Method: 191 patients (bipolar I disorder, manic episode) were randomized to 21 days double-blind treatment with quetiapine (QTP) (up to 800 mg/d) or placebo (PBO) and either Li or DVP (target trough serum concentrations 0.7-1.0 mEq/L and 50-100 μg/mL, respectively). Primary endpoint: change from baseline YMRS total score at Day 21 (QTP+MS vs PBO+MS; MITT, LOCF).

Results: 56 of 91 patients (61.5%) randomized to QTP+MS and 49 of 100 (49.0%) randomized to PBO+MS completed the study. By final assessment, QTP+MS-treated patients had a significantly greater reduction in YMRS compared with PBO+MS (–13.76 and –9.93; *P*=0.021). Significantly more quetiapine-treated patients achieved a response (≥50% decrease from baseline YMRS score) at Day 21 (QTP+MS 54.3%; PBO+MS 32.6%; *P*=0.005). The mean last-week quetiapine dose in responders was 580 mg/d. The most common adverse events (≥10%) noted in quetiapine-treated patients included somnolence, dry mouth, asthenia, and postural hypotension. Discontinuation due to adverse events was similar in each group.

Conclusions: Quetiapine as an adjunct to lithium or divalproex has superior efficacy in acute mania over treatment with mood stabilizer alone, and is well tolerated.

Source of Funding: AstraZeneca

Session I – 82

An Open Add-On Study of Oxcarbazepine Versus Divalproex to Treat Hypomanic Symptoms in Patients with Bipolar Disorder

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Background: The appropriate treatment and management of patients with bipolar disorder (BD) continues to be an active area of research. Few studies directly compare drugs from the same class. The primary objective of the study was to evaluate the effectiveness and tolerability of oxcarbazepine (OXC) to treat hypomania. The secondary objective was to compare, in a randomized group, the efficacy and tolerability of OXC to an established antimanic agent, divalproex (DVP).

Method: Bipolar I, II, NOS volunteers (n=30), currently hypomanic (Young Mania Rating Scale (YMRS) >12), signed informed consent and were randomized to receive OXC or DVP added to ongoing medications for 8 weeks. A blind rater evaluated clinical symptoms at regular intervals. No new medications could be added during the study; patients with continued or emerging symptoms were discontinued from the study. Baseline and periodic blood work was done to ensure patient safety and obtain serum levels for adequate dosing of DVP.

Results: Thirty volunteers were randomized to OXC (n=15; BDI=8; BDII= 4, BD NOS=3; female=9) or DVP (n=15; BDI=4; BDII=7; BD NOSfemale=9). Sample characteristics were relatively similar between groups. Mean age at entry was older for the DVP group.

At baseline visit YMRS mean for OXC subjects was 22 (n=15) and for DVP subjects 20 (n=14). At visit 4 (end of week 4) YMRS mean for OXC was 8 (n=12) and DVP was 6 (n=10). At baseline IDS-C mean was OXC = 25 and for DVP = 21. At visit 4 IDS-C mean was OXC = 15 (n=12) and DVP = 16 (n=10). Results from the full eight week period and dosing and serum levels will be reported.

Conclusions: OXC added to ongoing medication regimens for hypomania in patients with bipolar disorder was effective in decreasing hypomanic symptoms. OXC compared favorably with DVP, an established anticonvulsant antimanic agent.

Source of Funding: Novartis Pharmaceutical

Session I – 83

Adjunctive Topiramate to Mood Stabilizers in Patients with Bipolar I or II Disorder

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Objective: Evaluate safety/efficacy of adjunctive topiramate (TPM) to mood stabilizers (MS) in Bipolar I/II patients experiencing chronic mood instability.

Method: 109 outpatients (manic=3, hypomanic=8, mixed=42, depressed=56) with DSM-IV bipolar I/II, insufficiently managed with current MS, (CGI-S >= 4 & a YMRS >= 13 or MADRS >= 12), received open-label TPM for up to 16 wks, (25 – 400 mg/day) as add-on to MS (lithium, valproate or combination). MS and any concomitant psychotropics had to remain stable for ≥ 4 wks pre-entry.

Results: Mean modal dose of TPM = 145.0 mg (SD=91.8). TPM + MS achieved statistically significant improvements in YMRS and MADRS scores from wk 2 of treatment with hypomanic/depressed sub-groups = $p<0.05$ from wk 4 on YMRS, mixed group = $p<0.001$ from wk 2. Mixed and depressed sub-groups = $p<0.001$ on MADRS at wk 2. Significant improvement was also noted in CGI-S ($p<0.001$). Commonly reported AEs were headache (26%), nausea (22%), diarrhea (15%), fatigue (13%), somnolence (13%). Mean change in body weight for all patients at endpoint was = –1.8 kg. No clinically significant changes were observed in vital signs or laboratory parameters at endpoint.

Conclusion: Adjunctive TPM to MS is safe and effective in treating persons with bipolar disorder.

Source of Funding: This study was supported via funding provided by Janssen-Ortho, Canada

Session I – 84

Aripiprazole Vs. Haloperidol for Maintained Treatment Effects in Patients with Acute Mania

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Background: To compare the efficacy and tolerability of aripiprazole and haloperidol for the treatment of an acute manic episode in patients with bipolar I disorder.

Method: This 12-week, multicenter, double-blind study randomized 347 in- and outpatients with acute mania or mixed bipolar episodes to initial doses of either aripiprazole 15 mg/day or haloperidol 10 mg/day. Treatment doses could be titrated in weeks 1-3 to improve response and/or tolerability. The primary efficacy measure was response at Week 12, defined as ≥50% improvement from baseline in Young Mania Rating Scale (Y-MRS) score, and continuing on therapy.

Results: At Week 12, significantly more patients responded on aripiprazole (50%) than on haloperidol (28%; $p<0.001$). There were marked differences in long-term continuation rates for the two treatments (29.1% of patients remained in the haloperidol arm compared with 50.9% in the aripiprazole arm). Major reason for discontinuation in the haloperidol group was adverse events. Extrapyramidal Syndrome was reported in 36% of haloperidol patients versus 9% with aripiprazole. Neither drug was associated with weight gain during the study period.

Conclusion: Aripiprazole treatment led to significantly higher response rates and improved tolerability over haloperidol for maintained treatment of acute mania in bipolar I disorder at 12 weeks.

Source of Funding: Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc.

Session I – 85

Clinical Predictors of Response to Treatment in Bipolar I Disorder

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Objective: To examine predictors of response to maintenance treatment in bipolar I disorder.

Methods: 638 patients were randomized to 18 months of double-blind monotherapy with lamotrigine (n=280; 50-400mg/day fixed and flexible dose), lithium (n=167; 0.8-1.1mEq) or placebo (n=191). The effects of the total number of episodes and the number of manic or depressive episodes in the 1 and 3 years prior to treatment, early onset of illness, attempted suicide, time to randomization, and gender were examined against time to intervention for a mood episode using a Cox Proportional Hazard Model. Analyses were controlled by index mood and treatment.

Results: Overall, < 3 depressive episodes in the previous 3 years, later onset of illness, shorter time to stabilization, and lack of previous psychiatric hospitalization were predictive ($p<0.05$) of treatment response. By treatment, lithium response was associated with a late onset of illness (> age 20 years), lamotrigine response was associated with < 3 depressive episodes in the previous 3 years, and placebo response was associated < 3 manic episodes in the previous 3 years.

Conclusion: Response to maintenance treatment in bipolar I disorder appears related to severity of illness; response differs by treatment. These results may facilitate clinical decision-making in bipolar disorder.

Source of Funding: GlaxoSmithKline

Session I – 86

A Double-Blind Study Examining the Six-Month Outcome After Antipsychotic Discontinuation Following Acute Mania

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Background: Although conventional antipsychotic drugs are useful during the acute manic episode, their use during the continuation and maintenance phases of treatment has generally been discouraged because of the risk of the adverse events such as extrapyramidal symptoms, tardive dyskinesia and a negative impact on the course of the illness. However, most of these reports on the negative consequences with the long-term use of conventional antipsychotic drugs are based on naturalistic studies.

Methods: This is a randomized, double-blind, placebo-controlled, combination treatment study. Acutely manic or mixed bipolar patients were treated with perphenazine (4-64 mg per day) in combination with one or more mood stabilizers (within therapeutic doses) until remission was maintained for 2 weeks. Patients were then randomized to continue either with perphenazine or placebo in combination with their mood stabilizer for 6 months.

Results: After achieving remission from the acute manic episode, 19 subjects were randomized to perphenazine and 18 subjects to placebo in addition to their mood stabilizer. Kaplan-Meier survival analysis showed that subjects randomized to perphenazine compared to subjects randomized to placebo, had a shorter time to study discontinuation ($p=0.0256$), had a shorter time to relapse into depression ($p=0.028$), and were more likely to have depression (47% vs. 11%), akinesia (32% vs. 0%), and extrapyramidal symptoms (47% vs. 6%; all $p<0.05$).

Conclusions: The continued use of a conventional antipsychotic drug following remission from an acute manic episode was associated with a worse short-term outcome and an increased risk of neurological side effects.

Source of Funding: Founded by the National Alliance for Research on Schizophrenia and Depression (NARSAD)

Session I – 87

Previous Episode Burden and Response to Treatment in Bipolar I Disorder

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Objective: We examined the relationship between previous mood episode burden and response to lithium and lamotrigine in bipolar I patients enrolled in two large prophylaxis trials.

Methods: 638 patients were randomized to 18 months of double-blind monotherapy with lamotrigine (n=280; 50-400mg/day fixed and flexible dose), lithium (n=167; 0.8-1.1mEq) or placebo (n=191). The relationship between the number of mood episodes (manic + depressive, manic only, depressive only) in the 3 years prior to study entry and response to lithium or lamotrigine was examined using Kaplan-Meier estimates of time to intervention for a mood episode after 6 months of treatment. Hazard ratios were calculated using Cox proportional hazards model.

Results: Lithium (HR=0.597, 95% CI 0.445, 0.801) and lamotrigine (HR=0.645, 95% CI 0.495, 0.839) were effective regardless of episode burden. However, risk of intervention was generally highest for patients with more previous depressive episodes and lowest for fewer previous depressive episodes.

Conclusions: Burden of previous depressive but not manic episodes may be a predictor of outcome for bipolar I patients on mood stabilizer treatment.

Source of Funding: GlaxoSmithKline, Research Triangle Park, North Carolina

Session I – 88

Lamotrigine Use in Patients with Bipolar Disorder: Baseline Data from the STEP-BD 500

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Background: We describe the use of lamotrigine in the first 500 patients enrolled into the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study

Methods: Baseline data from the STEP-BD database were analyzed to assess current or lifetime lamotrigine use. Additional data collected include demographic and diagnostic information, concomitant use of mood stabilizers, history of rapid cycling, and history of antidepressant-induced mania or hypomania.

Results: Of the first 500 participants, 77 (15.4%) reported current lamotrigine use (mean dose: 258.12 mg/day), 52 (10.4%) reported prior lamotrigine use, and 371 (74.2%) reported no history of lamotrigine use. Of those taking lamotrigine at study entry, 74.0% were bipolar I, 24.7% were bipolar II. Most of this cohort was bipolar I, so looked at another way, of the patients with bipolar I **(**n=368), 15.5% were taking lamotrigine at study entry. Of the patients with bipolar II (n=115), 16.5% were taking lamotrigine at study entry. Of patients currently treated with lamotrigine, 48.1% reported a prior history of an antidepressant-induced switch to mania or hypomania, compared to 31.5% in patients who were never prescribed lamotrigine. Additionally, 68.8% had a history of rapid cycling compared to 48.0% in patients never prescribed lamotrigine. In the lamotrigine treated group, the mean number of concurrent mood stabilizers (defined here as lithium, valproate, or carbamazepine) used concurrently was 0.6 ($\pm$0.7). Concomitant antidepressant use was noted in 16.9% of lamotrigine-treated participants compared to 29.1% of participants with no history of lamotrigine.

Conclusion: Compared to participants with no history of lamotrigine use, a higher percentage of current lamotrigine-treated participants reported a history of rapid cycling, antidepressant-induced switch to (hypo) mania, supporting the hypothesis that lamotrigine is being used as an alternative to antidepressants in patients with bipolar disorder. Limitations of the cross-sectional dataset are noted.

Source of Funding: NIMH Contract

Session I – 89

Safety and Tolerability of Lamotrigine in Bipolar I Disorder

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Objective: Tolerability and safety are important considerations in optimizing pharmacotherapy for bipolar disorder. We examined the tolerability of lamotrigine in a large bipolar disorder clinical trial database.

Methods: Pooled safety data were analyzed from 8 placebo-controlled clinical studies, in which adults with DSM-IV bipolar disorder received lamotrigine at doses of 50-500mg (n=827) or placebo (n=685), for up to 18 months.

Results: Lamotrigine was well-tolerated with an adverse event profile comparable to placebo. The most common adverse event was headache (25% LTG, 21% PBO). Few patients experienced serious adverse events (8% LTG, 7% PBO), and the incidence of withdrawals due to adverse events was low (12% LTG, 10% PBO). Lamotrigine did not destabilize mood and was not associated with sexual side effects, clinically significant weight changes, or withdrawal symptoms. Serious rash was rarely (0.1%) reported.

Conclusions: Lamotrigine appears to be well tolerated as long-term maintenance treatment in bipolar I disorder.

Source of Funding: GlaxoSmithKline

Session I – 90

Burden of Manic Vs. Depressive Symptoms in Subjects with Bipolar Disorder

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Objective: To compare the burden of manic vs depressive symptoms in adults with bipolar disorder.

Methods: A self-administered survey was completed by a sample of subjects who had previously participated in a nationwide, general population, epidemiologic survey. Subjects were considered to have bipolar disorder (n=593) if they screened positive for bipolar disorder (MDQ+) or reported a physician diagnosis of bipolar disorder. Results were adjusted for sample demographics.

Results: Among MDQ+ subjects, depression caused more disruption in work (23% vs 16%, $p<0.01$), social (30% vs 20%, $p< 0.001$) and family functioning (32% vs 22%, $p<0.001$) than did mania. Depressive symptoms were significantly more likely to be associated with having arguments, not doing work well, feeling upset and being disinterested in work ($p<0.001$ for all measures) than were manic symptoms. Depressive symptoms were experienced for a higher percentage of days (44% vs 25%, $p<0.001$) and were more often disruptive (71% vs 56%) compared with manic symptoms.

Conclusions: Depression is associated with significantly greater psychosocial burden compared to mania, among subjects who screen positive for bipolar disorder.

Source of Funding: This research was supported by a grant from GlaxoSmithKline.

Session I – 91

Adjunctive Stimulant Use in Bipolar Disorder: Treatment of Residual Depression and Fatigue

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Background: Much of the disability, morbidity, and mortality of bipolar disorder is attributed to the depressed phase of the illness. Although a number of new treatments have emerged in recent years for mania, treatment options specifically for bipolar depression remain limited. Some evidence indicates that bipolar depression may be more responsive to dopaminergic agents, suggesting that adjunctive stimulant medication may be an effective treatment for bipolar depression. However, the use of stimulants in bipolar disorder has been limited due to fears of potential switching and stimulant abuse. The literature on the safety and efficacy of these medications in bipolar disorder is limited.

Methods: In order to evaluate the safety and effectiveness of psychostimulants in bipolar disorder, 8 consecutive cases (5 with bipolar I and 3 with bipolar II) who received adjunctive stimulants (methylphenidate or amphetamine) from a university-based research clinic within the last two years were retrospectively reviewed. Target symptoms for stimulant therapy included residual depression and medication-induced sedation. Those with comorbid attention-deficit-hyperactivity disorder were excluded from this series. The degree of clinical change of these target symptoms was estimated, and the Clinical Global Impression-BP Version scale was used to evaluate the overall severity of illness at baseline, 6 months after stimulant initiation, and at last visit.

Results: Overall, the patients showed moderate clinical improvement in their target symptoms (ranging from none to marked) and mild to moderate improvement of their overall bipolar illness. Side effects were minimal. All patients remained on the stimulant at their most recent clinical visit (mean duration 18 months; range 11 to 24 months). There was no evidence of stimulant-induced switching or abuse.

Conclusion: The use of psychostimulant augmentation in bipolar disorder may be a reasonably safe and effective therapeutic option for treating residual depression and medication-induced sedation, given adequate concomitant mood stabilization. Further studies on the use of adjunctive stimulants in bipolar disorder, including functional imaging studies, may serve to better delineate biological differences between unipolar and bipolar depression and to bring about more effective treatment options in bipolar depression.

Source of Funding: None

Session I – 92

Maintenance Treatments for Bipolar I Depression

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Objective: Lithium, used to treat bipolar mania, is believed to have antidepressant activity. We compared lithium and lamotrigine as maintenance treatments for bipolar I depression.

Methods: Placebo, lithium (Li), and lamotrigine (LTG) were studied as maintenance treatments for 18 months in bipolar I patients who were currently or recently symptomatic. Results from 2 clinical trials comprising 463 patients (index depressed) and 175 patients (index manic) were examined for incidence of depressive events, HAMD-17 scores, and DSM-IV depression events by treatment group and index mood episode.

Results: In recently manic patients, fewer lamotrigine than lithium-treated patients required intervention for depression (LTG 14%, Li 22%), reported depressive adverse events (LTG 0, Li 4%), had DSM-IV depression (LTG 10%, Li 17%), or had HAMD scores > 20 (LTG 3%, Li 11%). In recently depressed patients, depressive symptoms were similar between treatment groups: intervention for depression (LTG 34%, Li 38%), reported depressive adverse events (LTG 4%, Li 3%), DSM-IV depression (LTG 31%, Li 36%) or HAMD scores > 20 (LTG 22%, Li 18%).

Conclusions: Lamotrigine provided more protection against depressive symptoms than lithium, regardless of index mood. Results suggest that lamotrigine therapy should be considered during or shortly after stabilization of mania, before depressive symptoms occur.

Source of Funding: GlaxoSmithKline

Session I – 93

Physiologic Assessment of Antidepressant Drug Effects in Normal and Depressed Subjects

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Background: Certain medications (e.g., benzodiazepines) have characteristic physiologic signatures on quantitative electroencephalography (QEEG). The newer generations of antidepressants, however, never have been shown to have similarly robust and reproducible neurophysiologic effects. We conducted this study to determine the effects of venlafaxine in normal controls, and to compare effects in normal subjects with those previously observed in depressed subjects receiving either venlafaxine or fluoxetine (Cook et al., 2002).

Methods: Thirty-one normal volunteers were randomly assigned to double-blind treatment with either venlafaxine in escalating doses up to 150 mg for four weeks, or placebo. QEEG studies were performed starting 48 hours after randomization and then weekly thereafter.

Results: There was no effect of venlafaxine on QEEG power in normal subjects. There were, however, significant decreases in QEEG cordance, a measure that has stronger associations with cerebral perfusion than traditional power measures. Cordance decreased significantly in the right frontocentral ($p=.006$) and left parietal regions ($p=.034$) after 48 hours of treatment in those subjects receiving medication. The decreases in normal subjects were of similar magnitude to those seen in 24 depressed subjects who received double-blind treatment with either venlafaxine or fluoxetine. Logistic regression using right frontocentral and left parietal cordance as predictors accurately identified treatment condition in 74.2% of the normal subjects after 48 hours (two doses).

Conclusions: Results indicate that cordance can be used to detect antidepressant physiologic effects in normal or depressed subjects. It may be possible to utilize cordance after brief antidepressant treatment in normal subjects to screen putative antidepressant compounds.

Source of Funding: Supported in part by Lilly Research Laboratories and Wyeth-Ayerst Pharmaceuticals

References:

Cook IA, Leuchter AF, Witte EA, Stubbeman WF, Abrams M, Rosenberg S. Early changes in prefrontal activity characterize clinical responders to antidepressants. Neuropsychopharmacology 27:120-131, 2002.

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Session I – 94

^{1}H MRS Study of In Vivo Effects of Lithium on N-Acetyl Aspartate (NAA) Cortical Levels in Healthy Human Subjects

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Background: Recent preclinical studies suggested that lithium has neuroprotective effects, which could be possibly related to its therapeutic actions. A prior study (Moore et al, 2000) identified increased levels of N-acetyl aspartate (NAA) in various cortical regions in bipolar patients and healthy controls after treatment with lithium for 4 weeks. Here we attempted to replicate those findings by measuring the NAA levels in dorsolateral prefrontal cortex (DLPFC) in healthy adult volunteers, before and after lithium administration, with vivo ^{1}H magnetic resonance spectroscopy (MRS).

Methods: Twelve healthy individuals (mean age±S.D.=25.0±9.8) underwent a ^{1}H-MRS session at baseline and after 4 weeks of lithium administration at therapeutic doses. ^{1}H-MRS was performed with a GE-Signa 1.5T scanner, utilizing two 8cc voxels placed in the right and left DLPFC, with a STEAM sequence (TE=20ms, TR=1.5sec, 300-acquisitions).

Results: The levels of NAA after lithium administration did not differ significantly compared to baseline in either right or left DLPFC (Paired t-tests, $p>0.05$). Other major metabolites (CHO, PCr+Cr, INO) did not differ significantly after lithium treatment (Paired t-tests, $p>0.05$).

Conclusion: Our study did not replicate prior findings of increased NAA levels in cortical regions after lithium treatment in healthy individuals. The findings of increased NAA cortical levels have previously been interpreted as direct evidence for lithium having detectable neuroprotective effects. Our findings may indicate that such effects are detectable in patients, where regional gray matter content may be reduced, but that they may not be present in healthy controls receiving this medication. Future longitudinal studies will be needed to investigate whether chronic lithium treatment in bipolar patients may modulate NAA regional cortical levels, and examine the relevance that such effects may have for the therapeutic actions of lithium.

Source of Funding: This study was partly supported by MH-01736, MH-30915, and NARSAD.

Session I – 95

Design Decisions in Abuse Liability Studies

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Psychoactive medications, including those to treat depression, anxiety, pain, ADHD, and dependence, require assessment of abuse liability (including dependence potential). Clinical analogues of abuse liability, unlike those of most other safety threats, can be experimentally produced in a relatively rapid, safe, and reliable manner. The fundamental assumption is that drugs acutely perceived as similar to reference abusable drugs will share their abuse liability. Studies implementing this require design decisions not ordinarily encountered in other clinical trials.

We illustrate these issues with a recent trial comparing placebo, compound B (a novel dopamine and norepinephrine uptake inhibitor, 5mg, 10mg, and 20mg), and d-amphetamine (10mg and 20mg). Twelve subjects completed the trial, each receiving all six treatments in counterbalanced order with 72-hour washout.

Subjects had experience with psychoactive drugs (for ethical as well as scientific reasons) and demonstrated drug responsiveness to 200 mg caffeine versus placebo in a pretest. No validation of the pretest compared those who passed and failed, but a previous report (Busto et al 1999) showed clear differences when similar groups were retested. A post-report reanalysis revealed two subjects unresponsive to any drugs on a key instrument (subjective dollar value of the drug); more carefully constructed entrance criteria might have prevented this.

The standard Cole/ARCI scale, which distinguished everything except B 5mg from placebo, did not distinguish B 20mg from d-amphetamine 20mg ($p<0.05$). The subjective value measure distinguished only d-amphetamine 20mg from placebo but also distinguished it from all doses of B. Compound-versus-placebo and compound-versus-compound criteria would lead to different choices of primary measure for any new study. Had the design included a non-abused, mild stimulant (such as pseudoephedrine) distinguishable from both placebo and d-amphetamine, the difference between placebo and B could perhaps have been interpreted more favourably.

A wider range of doses could have risked safety at the high end, although larger doses might have revealed a ceiling effect for only one compound. An alternative design starts with middle doses and goes up or down depending on individual tolerance, but this complicates study logistics and subsequent analysis.

Source of Funding: Supported by Ventana Clinical Research Corporation

Session I – 96

Lack of Effect of Bupropion SR on Blood Pressure in Hypertensive Patients

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Background: Bupropion SR (BupSR) did not cause clinically significant changes in mean blood pressure (BP) in clinical trials, but there have been isolated reports of BupSR-associated BP increases occurring primarily among smokers. This randomized, double-blind study was designed to examine effects of BupSR on BP in mildly hypertensive patients.

Methods: Non-depressed outpatients with untreated Stage I hypertension received BupSR 150mg, 300mg, 400mg, or placebo for 4 weeks (n=74/group).

Results: BupSR did not differ from placebo in the primary endpoint of mean difference between pre- and post-treatment clinic diastolic or systolic BP (DBP, SBP). For BupSR 150mg, 300mg, 400mg, and placebo, the respective differences were -2.3, -1.9, -1.6, -2.4 mmHg for DBP and -6.5, -4.0, -5.0, -6.5 mmHg for SBP. The percentage of patients with any clinically significant increase in either DBP or SBP (increase of 6 or 10 mmHg, respectively) did not differ between any BupSR group (20% each group) and placebo (15%; p=0.52 each comparison). In addition, BupSR did not differ from placebo in mean change from baseline in average 24-hour BP at day 28. For each BupSR dose, changes in DBP were (respectively) 0.2, 2.3, 2.1 vs. 0.04 mmHg for placebo, and for SBP, 0.7, 1.8, 1.1 vs. -0.6 mmHg for placebo.

Conclusions: BupSR, a norepinephrine and dopamine reuptake inhibitor (NDRI), did not affect BP in this controlled study.

Source of Funding: GlaxoSmithKline

Session I – 97

Safety of Selegiline Transdermal System in Long-Term Prevention of Relapse of Depression

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Background: Selegiline, a selective MAO-B inhibitor, has been formulated as a transdermal patch for treatment of major depressive disorder (MDD) without requiring dietary restrictions. The long-term safety of this selegiline transdermal system (STS) was evaluated in a 1-year, double-blind, placebo-controlled trial of safety and efficacy for prevention of relapse in patients with MDD.

Methods: 321 patients in remission from MDD by previous treatment with STS were randomized to treatment with the STS 20 mg/20 cm^2 or placebo daily for up to 52 weeks (STS, 158; placebo, 163). A tyramine-restricted diet was not observed, but drugs known to interact with MAO inhibitors were prohibited. Safety, vital signs, and efficacy were measured at screening, baseline, and periodically thereafter. Relapse of MDD was defined as 2 consecutive measurements of HAM D-17 ≥14 and CGI-s ≥3 with ≥+2 change from baseline.

Results: Long-term treatment data suggest that STS is safe and well tolerated. 21 (13.2%) STS-treated and 11 (6.7%) placebo-treated patients discontinued treatment due to AE(s), primarily for application-site reactions (ASRs) (*P*=0.038). 3 patients (STS, 2; placebo, 1) discontinued for hypertension, but no acute hypertensive episodes or serious drug-drug interactions were reported. The most common treatment-emergent AEs were ASRs, headache, and insomnia. No clinically meaningful differences were reported for clinical laboratory, vital signs, physical examinations, or ECG results. Relapse rates in STS subjects were lower than observed in placebo-treated subjects (6 months, 25/149 [16.8%] vs 48/163 [29.4%], respectively [*P*=0.005]; 1 year, 25/149 [16.8%] vs 50/163 [30.7%], respectively [*P*=0.003]). Kaplan-Meier survival analysis also favored STS over placebo maintenance treatment (*P*<0.006).

Treatment-Related AEs

	STS Group (N=158)	**Placebo Group (N=163)**	***P* Value**
AEs, % subjects	54.4	41.7	0.0256
ASR	15.2	3.7	0.0004
Headache	12.0	9.8	0.5928
Insomnia	10.1	6.7	0.3178
Nervousness	5.1	3.7	0.5942
Depression	2.5	3.1	1.0000
Dizziness	2.5	5.5	0.2577
Hypertension	2.5	1.8	0.7198
Palpitation	1.9	3.1	0.7234
Tachycardia	1.3	0.6	0.6180
Peripheral edema	1.3	0.0	0.2415
Atrial fibrillation	0.6	0.0	0.4922
Postural hypotension	0.6	0.6	1.0000

Conclusion: STS, a unique MAOI, appears to be safe, effective, and well tolerated in sustaining antidepressant response of patients with major depression over a 1-year treatment period.

Source of Funding: Somerset Pharmaceuticals, Inc.

Session I – 98

Preliminary Results from the ARISe-RD (Risperidone Augmentation in Resistant Depression) Trial

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Background: Increasingly, atypical antipsychotics are seen as safe and efficacious augmenting agents in depression, supporting the development of the large, international, multi-center ARISe-RD trial.

Methods: In ARISe-RD, subjects historically failing ≥1 antidepressant plus a prospective, 4-6 week citalopram course, receive open-label risperidone augmentation for 4 weeks (0.25-2 mg/day), followed by a placebo-controlled relapse prevention phase for risperidone-remitters.

Results: Interim data include 41 enrolled subjects. The citalopram non-response rate was 80%. Subjects receiving risperidone augmentation (n=33) had significant improvement in HAM-D and MADRS-total scores (21.8±5.7 to 11.0±7.3, 30.2±7.2 to 16.0±10.4, respectively; $P<0.001$), with mean percentage reductions of 49.9% on the HAM-D and 47% on the MADRS ($P<0.001$). Significant improvement was noted by Day 4 of augmentation (MADRS-total: -3.6±7.2, $P<0.01$). Improvements in global impression ratings were also present (CGI-Severity=moderate or worse: 80.0% at baseline; 31.0% at endpoint). Prospectively-defined responses of >20%, >30%, >40%, or >50% in MADRS were achieved by 81.8%, 63.6%, 54.5%, and 48.5% of patients, respectively. Mean change reductions in movement disorder ratings were present (SAS -0.15; $p=0.26$, BAS -0.03; $p=0.87$).

Conclusion: Initial results from this large-scale examination in resistant depression suggest augmentation with low-dose risperidone provides rapid, robust effects in improving depressive symptoms without evidence for movement disorders liability.

Source of Funding: Supported by Janssen Pharmaceutica Products, LP

Session I – 99

Adjunctive Ziprasidone in Treatment-Resistant Depression: A Pilot Study

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Objective: To evaluate the efficacy of ziprasidone as adjunctive therapy in treatment-resistant major depression without psychotic features.

Methods: Enrolled patients had a history of failure to respond to at least 4 weeks' adequate antidepressant therapy with ≥ non-SSRI or SSRI only. After a 1-week screening period, 64 patients entered a 6-week open trial of sertraline 100-200 mg/day. Nonresponders (≤ 30% improvement on MADRS, CGI-S ≥ 4, and meeting DSM-IV major depression criteria) were randomized to 8 weeks of open treatment with sertraline monotherapy (n=20) or combination therapy with ziprasidone 40 mg or 80 mg BID (n=40).

Results: At endpoint, patients with a history of non-SSRI treatment resistance who received combination therapy (n=27) demonstrated significantly greater improvement versus those patients who received monotherapy (n=13) in MADRS ($P<0.05$), the primary efficacy variable, and in HAM-D 17 ($P<0.05$), CGI-S ($P<0.01$), and CGI-I ($P<0.05$). Among patients with history of SSRI resistance only, improvement with combination therapy (n=14) did not reach significance versus sertraline monotherapy (n=7). No specific safety concerns were observed with combination therapy.

Conclusions: In patients with major depression and a history of non-SSRI treatment failure, combination therapy with ziprasidone and sertraline demonstrated greater efficacy than sertraline monotherapy.

Source of Funding: Pfizer, Inc.

Session I – 100

Analysis of Olanzapine/Fluoxetine Combination in the Treatment of Rapid-Cycling Bipolar Depression

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Background: Rapid cycling occurs in 13-20% of bipolar disorder patients[1] and is typically associated with poor response to traditional mood stabilizers. Antidepressant monotherapy is discouraged in such patients due to potential cycle acceleration and treatment-emergent mania. Because these patients spend a substantial amount of time in the depressed state, there remains a need for an antidepressant treatment that is effective in rapid-cycling patients. This study compares olanzapine/fluoxetine combination (OFC) with olanzapine monotherapy (OLZ) or placebo (PLA) in the treatment of patients with rapid-cycling bipolar depression.

Methods: 833 subjects with bipolar depression (baseline MADRS total scores ≥20) were enrolled in this 8-week double-blind study and randomized to OFC (6/25, 6/50, or 12/50 mg/day, n=86), OLZ (5-20 mg/day, n=370), or PLA (n=377). The current analyses evaluated a subset of 315 patients with rapid-cycling histories (n=37 OFC; n=140 OLZ; n=138 PLA). Depression and treatment-emergent mania were evaluated using the MADRS and YMRS, respectively.

Results: At 7 days, both OFC and OLZ demonstrated significantly greater improvement in MADRS total score than PLA. However, only OFC maintained this effect at all subsequent visits. OFC was significantly better than OLZ at weeks 4, 6, and 8. Mean decrease in MADRS total score at the acute phase endpoint was (OFC -15.7 vs. OLZ -9.5, p=.007; vs. PLA -9.8, p=.005). OFC also showed significantly higher response rates at endpoint (OFC 77.8% vs. OLZ 35.7%, p<.001; vs. PLA 39.4%, p<.001) and remission rates (OFC 77.8% vs. OLZ 54.1%, p=.001; vs. PLA 49.5%, p=.007). Treatment-emergent mania (baseline YMRS < 15 and $\underline{\geq}$ 15 at any subsequent visit) did not differ among therapy groups (OFC 9.7%, OLZ 8.5%, PLA 4.2%, p=.257).

Conclusion: Rapid-cycling subjects acutely treated with OFC experienced greater improvement in depressive symptoms and higher response and remission rates than subjects on olanzapine or placebo. OFC treatment was not indicative of increases in cycling beyond that seen with placebo or olanzapine.

Source of Funding: Eli Lilly and Company

[1] Calabrese JR, Shelton MD, Rapport DJ, Kujawa M, Kimmel SE, Caban S. (2001). Current research on rapid cycling bipolar disorder and its treatment. *J Affect Disord*. 67: 241-255.

Session I – 101

Initiating Modafinil with SSRI Enhances Degree and Onset of Therapeutic Effects in Depression

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Objective: Responder rates to open-label selective serotonin reuptake inhibitor (SSRI) treatment in major depressive disorder (MDD) is 10.6%, 32.4%, and 48.4% at weeks 2, 4, and 6, respectively.[1] In addition, MDD symptoms such as fatigue, lack of energy, and sleepiness may not respond to or may be exacerbated by some antidepressants. The wake-promoting agent modafinil works selectively through the sleep-wake centers of the brain to improve wakefulness and reduce fatigue in various disorders. In MDD patients with residual fatigue and an incomplete response to antidepressants, modafinil improved wakefulness and reduced MDD symptoms within 1-2 weeks, suggesting that modafinil may be useful in SSRI therapy initiation to speed the onset of treatment response. This open-label study is the first to evaluate modafinil combined with SSRIs at treatment initiation in MDD patients with fatigue.

Methods: Patients with MDD and symptoms of sleepiness and fatigue who were free from antidepressant therapy for ≥4 weeks were started on a combination of modafinil and SSRI therapy. Modafinil was initiated at 100 mg/day for 3 days and then titrated to 200 mg/day. SSRI therapy was either fluoxetine 20 mg/d or paroxetine 20 mg/d for 6 weeks. Assessments included the Hamilton Depression Scale (HAMD-31, HAMD-21), Epworth Sleepiness Scale (ESS), and Fatigue Severity Scale (FSS). Adverse events were monitored.

Results: 14/18 evaluable patients (78%) completed the study. The average baseline HAMD-31 score was 31.72±7.28. Modafinil combined with fluoxetine or paroxetine significantly improved total HAMD-31 scores within 1 week of initiation (mean: -9.47±12.06; $P<.01$). Improvement was maintained throughout the study (mean: -23.06±13.55; $P<.01$). Response, defined as a 50% reduction in HAM-D scores, was achieved by 44.4%, 64.3%, and 80% by week 2, 4, and 6, respectively. In addition, 12%, 39%, and 60% of patients met HAMD-21 criteria for remission (score ≤7) by week 1, 2, and 6, respectively. Modafinil significantly improved wakefulness (ESS) beginning at week 1 and reduced fatigue (FSS) beginning at week 2 ($P<.05$). Modafinil was well tolerated in combination with the SSRIs. Three patients discontinued because of adverse events.

Conclusion: Modafinil combined with SSRIs may enhance the rate and degree of benefit achieved in MDD patients.

Source of Funding: Funded by Cephalon, Inc.

References:

1. Nierenberg AA, Farabaugh AH, Alpert JE, et al. Timing of onset of antidepressant response with fluoxetine treatment. Am J Psychiatry. 2000;157:1423-1428.

Session I – 102

The Impact of Augmentation and Switching on Costs of Treatment of Depression

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Background: Controlled double-blind studies indicate that about 30% of depressed patients do not respond to current therapies. Of those that respond, not all patients who are treated with antidepressants are likely to respond to the same therapy. A patient who fails to respond to the first treatment attempted is highly likely to respond to a different treatment. Some patients may achieve only a partial response or discontinue treatment owing to side-effects and require use of a second antidepressant. Thus treatment of depression may require the use of combination therapy or necessitate a switch between alternative antidepressants.

Objective: The objective of this study is to estimate the impact of early antidepressant discontinuation, switching/augmentation on costs in the treatment period and 1-year post-treatment period.

Methods: 2655 patients diagnosed with major depressive disorder between 6/95-12/96, prescribed an SSRI within 30 days of diagnosis and enrolled in a national managed care plan were followed up for one year after discontinuation of anti-depressant treatment. A treatment algorithm based on prescription refill patterns was used to identify completers, switchers, augmenters and multiple antidepressant users (> 2 antidepressants). Multivariate linear regression with log transformation of costs was the primary method of analysis. Age, gender, regional differences, comorbidities at baseline, initial anti-depressant used, duration of therapy, physician specialty and subtype of depression were controlled in the model. Smearing estimators were used to retransform the adjusted costs from log-scale to dollar scale.

Results: 21% of the patients required use of a second antidepressant during course of treatment. Switchers and augmenters incurred higher costs in the treatment and post-treatment period as compared to patients who completed therapy on index drug. The adjusted mean 1-year post-treatment costs for switchers, augmenters and completers were $3415, $4938 and $2728 respectively (F=40.29, p=0.000). Similarly the treatment costs/month during the depressive episode for switchers, augmenters and completers were $531, $592 and $421 respectively (F=194.37, p=0.000).

Conclusion: Switching and augmentation impose a significant economic burden on treatment of depression. There is a need for new antidepressants that are independently effective in a heterogenous population reducing the need to switch/augment antidepressant therapy.

Source of Funding: GlaxoSmithKline

Session I – 103

Escitalopram is Effective in Relapse Prevention in Social Anxiety Disorder

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Introduction: Escitalopram is the most selective SSRI, whose efficacy and safety in the treatment of MDD have been established.

Objectives: To determine the efficacy of escitalopram 10-20mg/day in preventing relapse in patients with social anxiety disorder (SAD).

Methods: This study was conducted in outpatients (18-80 years) with a primary diagnosis of generalised SAD (DSM-IV) and an LSAS ≥ 70. After 12 weeks of open-label treatment (10-20mg/day escitalopram), patients responding (CGI-I of 1 or 2) were randomised to 24 weeks of escitalopram (n=190) or placebo (n=181) treatment, to assess their relapse rate. The initial dose of 10 mg/day escitalopram could be doubled to a maximum of 20 mg/day, if clinically indicated, at Week 2, 4, or 8. Relapse was either an LSAS increase ≥ 10 or discontinuation due to lack of efficacy.

Results: The risk of relapse was 2.8-times higher for placebo-treated patients than for patients continuing escitalopram treatment (log-rank, $p<0.001$). The cumulative relapse rate at Week 24 was 23% for the escitalopram group versus 56% for the placebo group. The favourable long-term side-effect profile of escitalopram treatment was confirmed, with only 4% of escitalopram-treated patients withdrawing due to adverse events.

Conclusion: Escitalopram 10-20mg/day is highly effective in preventing relapse in patients with SAD.

Source of Funding: Supported by H. Lundbeck A/S

Session I – 104

Relapse Prevention with Gepirone-ER in Outpatients with Major Depression

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Objective: To evaluate the long-term efficacy of gepirone-ER (a 5-HT_{1A} agonist), a relapse prevention study was undertaken.

Methods: This was a multi-center, randomized, placebo-controlled trial of gepirone-ER for the prevention of relapse in patients with recurrent major depression. Eligible patients entered an 8 – 12 week open-label phase. Patients initially received a dose of 20 mg/day and were titrated to a dose of 40-80 mg/day of gepirone-ER. Patients who achieved remission (HAMD-17 score of ≤ 8) at weeks 8 or 12 were randomized to gepirone-ER 40 – 80 mg/day or placebo for 40 – 44 weeks. For the primary endpoint, relapse was defined as a HAMD-17 score of >16 or discontinuation for lack of efficacy.

Results: In total, 303 completed the open-label phase and 250 fulfilled the criteria for remission. For the double-blind continuation phase, 126 patients were randomized to gepirone-ER and 124 to placebo. The relapse rate was 23.0% with gepirone-ER and 34.7% with placebo ($p = 0.025$ vs. placebo). During the open-label phase, adverse events that occurred in more than 5% of subjects were headache (12.9%), nausea (15.7%), dizziness (13.1%), insomnia (6.2%), and vertigo (6.0%). Gepirone-ER did not appear to cause significant weight gain over 40 weeks of treatment.

Conclusion: Gepirone-ER 40 to 80 mg/day is effective for relapse prevention in patients with recurrent major depression and is well tolerated during long-term treatment.

Source of Funding: Funded by NV Organon

Session I – 105

Olanzapine Versus Lithium in Relapse Prevention in Bipolar Disorder: A Randomized Double-Blind Controlled 12 Month Clinical Trial

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Purpose: This is the first randomized double-blind comparison of the efficacy and safety of olanzapine and lithium in the prevention of relapse into a manic, mixed, or depressed bipolar episode.

Methods: 543 patients with a diagnosis of bipolar I disorder, manic or mixed type, with a history of at least 2 manic or mixed episodes within 6 years, and a YMRS total score ≥ 20 entered the study and received open label combination therapy of olanzapine and lithium for 6-12 weeks. Of these, 431 patients met symptomatic remission criteria (YMRS total score ≤12 and HAMD-21 total score ≤ 8) and were randomized to monotherapy with either olanzapine (N=217) (5-20 mg/d) or lithium (N=214) (titrated to a therapeutic serum level of 0.6 to 1.2 mEq/L in a dose range of 300-1800 mg/d) for 52 weeks of double-blind treatment.

Results: Significantly more olanzapine-treated patients (46.5%) completed the 52-week trial than those on lithium (32.7%; *P*=.004). Relapse to an affective episode, defined as YMRS total score ≥15 and/or HAMD-21 total score ≥15, occurred in 30.0% of olanzapine-treated and 38.8% of lithium-treated patients (*P*=.055). Olanzapine-treated patients had a statistically significantly lower incidence of relapse into a manic episode than lithium-treated patients (14.3% vs 28.0%, respectively, *P*<.001), and both groups had similar incidences of relapse into a depressive episode (16.1% vs 15.4%, respectively, *P*=.895). The incidence of hospitalization for an affective episode was significantly greater for lithium-treated compared with olanzapine-treated patients (22.9% vs 14.3%; *P*=.026). The rates of discontinuation due to adverse events were 18.9% for the olanzapine group and 25.7% for the lithium group (*P*=.105). Weight gain across open-label and double-blind therapy phases was statistically significantly greater in the olanzapine group compared to the lithium group (1.79 kg vs -1.38 kg, respectively, *P*<.001).

Conclusion: Olanzapine and lithium both appear to effectively and safely prolong remission in bipolar disorder, yet more patients remained on olanzapine throughout this year-long study and it was more effective than lithium in preventing relapse into mania.

Source of Funding: Eli Lilly and Company

Session I – 106

Risperidone Prevented and Restored the Haloperidol-Induced Reduction in Expression of Nerve Growth Factor and Choline-Acetyl Transferase in Basal Forebrain-Cortical Projections in Rat

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Background: Haloperidol (HAL) but not risperidone (RIS) or clozapine (CLOZ) was found to damage the brain cholinergic activity, which paralleled the impaired cognitive performance after 45 days in rats. Later, the cholinergic changes were found to correlate with the changes in nerve growth factor (NGF), which has been shown to regulate the brain cholinergic activity and thereby cognition in mammals. Since the use of RIS or CLOZ is preferred over HAL in patients, effects of their pre- or post-treatment were investigated on the HAL-induced parallel alteration in the expression of NGF and choline acetyltransferase (ChAT, cholinergic marker) in nucleus basalo-cortical cholinergic pathway.

Methods: Male Wistar rats (250-300gm) were divided into 8 groups of 6-8 animals each: CONT = vehicle; HAL, RIS, CLOZ = 2, 2.5 and 20 mg/kg/day, respectively; Post-treatment = HAL/RIS, HAL/CLOZ; Pre-treatment = RIS/HAL, CLOZ/HAL. Duration of each treatment was 45 days. Levels of NGF protein were determined by Enzyme Liked ImmunoSorbent Assay (ELISA, pg/mg protein), NGF and ChAT alone, and co-localization by immunohistochemistry.

Results: As expected, HAL but not RIS or CLOZ reduced the levels of NGF and ChAT in nucleus basalis and cortex. However, pre-treatment with either of these prevented and post-treatment markedly restored both the NGF ($P<0.05$ vs HAL) and ChAT ($P<0.05$ vs HAL) in nucleus basalis and basalo-cortical projections.

Conclusions: These findings support the proposed neuroprotective effects of RIS and CLOZ through their effects on expression of NGF and thereby preservation of basalo-cortical cholinergic activity and the cognitive performance.

Source of Funding: Janssen Pharmaceutica Products, L.P.

Session I – 107

Prophylactic Treatment of Recurrent Depression: A Randomized Controlled Trial of Sertraline in Remitted Patients

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Objective: To determine if sertraline can prevent the occurrence of a new depressive episode in highly recurrent patients currently in remission.

Methods: It was a 20-month, randomized, placebo-controlled double-blind, multi-center French study. Patients presenting at least 3 major depressive episodes (MDE) within the last 4 years and currently in full remission were eligible. Patients initially entered a two-month single-blind placebo period (n=371) to confirm the stability of the remission, then were double-blind randomized (n=288) to 50 mg or 100 mg of sertraline (Ser) or placebo (Pbo) for 18 months. The primary criterion was the occurrence of a depressive recurrence according to investigator opinion and/or DSM IV criteria. Sensibility multiple analysis on MADRS thresholds has been performed to confirm the recurrence independently of primary criteria.

Results: During the double-blind prophylactic phase, 123 over 288 patients discontinued, including 65 for recurrences. Recurrences were significantly (P=0.002) lower in the Ser group compared with Pbo (ser 50 + 100 mg 32/199 [16.1 %] Pbo 33/99 [33.3 %)]. According to sensibility analysis, percentages of recurrence for each final MADRS cut-off scores (18 to 22) were significantly ($p \leq 0.04$) lower in sertraline group compared to placebo; 28.7%, 28.7, 28.7%, 28.7% and 27.7 % for Pbo compared to 16.0%, 16.0%, 14.4%, 13.8% and 12.2% for Ser, according to thresholds of 18, 19, 20, 21 and 22 on MADRS. Globally, sertraline was well tolerated; however, the number of adverse events was slightly lower in the 50 mg group .

Conclusion: This study is the first one to prove a significant efficacy of an antidepressant i.e. sertraline in the prevention of recurrences of depressive episodes. According to MADRS cut-off score, percentages of recurrence were stable in the placebo group, comparing to a gradient of percentage in sertraline group.

Source of Funding: Supported by Pfizer France.

Session I – 108

Bupropion SR's Pharmacokinetics and Antidepressant Response in Juvenile Depression

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Objective: To explore potential correlations at steady state between pharmacokinetic variables of bupropion sustained release (SR) and antidepressant response in a sample of children and adolescents.

Methods: Subjects (Ss) were 7 boys and 8 girls (mean age: 15.3 ± 1.7 yrs) prescribed bupropion SR for Major Depression (n=5) or Depressive Disorder NOS (n=10). Twelve Ss also had comorbid ADHD. All took bupropion SR in morning daily doses of either 100 mg (n=9) or 200 mg (n=6) for ≥ 14 days (mean duration: 26 ± 24 days). Four Ss were studied at both doses. Ss stayed 24 hrs in an inpatient pharmacokinetic lab to have serial blood draws every 1.5 to 3 hrs from an IV port. Plasma concentrations of bupropion (BUP) and its metabolite hydroxybupropion (HB) were examined at intervals from 1 to 24 hours after the morning dose (C1 to C24), along with maximum concentrations (Cmax) and areas under the curve for 24 hrs (AUC24), to explore correlations with clinical response, rated by the treating psychiatrist using the Clinician's Global Impression's Improvement scale (CGI-I) (1 = very much improved to 7 = very much worse).

Results: Findings with BUP's kinetic variables are reported here. Using Fisher's exact tests, responders (n=8), defined as having CGI-I ≤ 2, differed significantly from non-responders (n=7) in the frequency that their BUP levels exceeded the sample's median levels at 6 and 7.5 hrs: C6 ≥ 50 ng/ml (p=.03), and C7.5 ≥ 36 ng/ml (p=.01). The table below shows Pearson correlations between CGI-I ratings of depressive response and BUP's kinetic variables (with p values immediately below):

	AUC24	C6	C7.5	C9	C10.5	C12	Cmax
CGI-I	-0.49	-0.65	-0.66	-0.49	-0.55	-0.27	-0.60
	.07	.008	.008	.07	.04	.32	.02

Conclusions: BUP levels during the early elimination phase may be useful correlates of antidepressant response in youth treated with bupropion SR, pending replication of these findings in controlled, double-blinded conditions.

Sources of Funding: NIMH grants N01 MH070008, P30 MH055123, R25 MH060473, and K23 MH065375.

Session I – 109

Pulse-Loaded Intravenous Clomipamine for Treatment-Resistant OCD

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Background: From 20% to 40% of patients with obsessive-compulsive disorder (OCD) fail to respond adequately after two or more oral trials of serotonin reuptake inhibitors (SRIs). In a double-blind pilot study of intravenous versus oral pulse-loaded clomipramine (CMI) for such patients, intravenous CMI was clearly superior. We are conducting a multi-site, double-blind study to test two hypotheses: 1. pulse-loaded intravenous CMI for 2 days will have a more rapid onset of action (by day 6) in treatment-resistant OCD than identical doses of oral CMI; and, 2. Pulse-loaded intravenous CMI will produce a higher responder rate than pulse-loaded oral CMI, i.e., will be more effective, in patients receiving 12 weeks of follow-up oral CMI treatment.

Methods: We are enrolling patients who have failed at least two adequate SRI trials and have Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores of at least 21. In a double-blind, double-dummy design, they receive 150 mg of oral or intravenous CMI on day 1 and 200 mg on day 2; on day 6 they start 12 weeks of open-label oral CMI (200 mg/d, titrated rapidly to 250 mg/d).

Results: Of the first 23 patients, 3 (13%) were responders (Y-BOCS decrease of at least 25%) at day 6, 3 more (13%) after one week of oral CMI, 8 more (35%) by end of week 4, and 1 more by end of week 6 (total = 15, or 65%). Four lost the response after week 4 and three withdrew due to adverse events. Three responders had previously failed an adequate oral CMI trial. The blind will be broken after 30 patients complete the trial.

Discussion: Animal studies suggest that high plasma levels of tricyclic antidepressants such as CMI are more powerful than lower levels in activating certain neuronal genes. Compared with oral loading of CMI, intravenous loading produces plasma CMI levels that are 4 to 14 times higher, which may explain its more rapid onset of action and its greater effectiveness.

Conclusion: If all or most of the 15 responders received intravenous pulse loaded CMI, this treatment will have been shown to be highly effective in treatment-resistant OCD.

Source of Funding: National Center for Research Resources (NCRR) and Stanford University

Session I – 110

Switching to Divalproex Extended Release in Patients with Bipolar Disorder

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Background: The new divalproex extended release (ER) formulation may improve patient compliance, decrease peak-related side effects, and simplify serum level monitoring and interpretation. The objectives of this study are to assess the pharmacokinetics, side effects, and short-term effectiveness of divalproex ER.

Methods: This study is an investigator-initiated, single site, crossover study of divalproex to divalproex ER in patients with stable bipolar I or II disorder. Pharmacokinetics (+12hr, +16hr, +20hr, +24hr valproic acid serum (VPA) levels following last dose) were obtained on 1) divalproex in split dose, 2) total daily divalproex given at bedtime (qhs), 3) divalproex ER 1:1 crossover dose ; and 4) divalproex ER 1:1 plus 500mg dose. Final dose was maintained for one month. Symptoms were assessed with established rating scales at each visit.

Results: Six males (mean age 51.5 ± 9.3 SD) have completed the study to date. Baseline mean±SD dose (mg/d); a.m. and p.m. trough VPA levels (μg/ml) for each were respectively:

- 1333 ±516mg/d, 51 ±19.60, and 50.58 ±19.73 for divalproex split dose qam and qhs;
- 1333 ±516mg/d, 68.07 ±17.45, and 39.63 ±13.79 for divalproex total dose qhs;
- 1333 ±516 mg/d, 65.8 ±20.77, and 50.0 ±12.81 for divalproex ER (1:1) qhs;
- 1833 ±516 mg/d, 78.37 ±28.68, and 52.88 ± 29.19 final divalproex ER (1:1+500mg) qhs.

VPA levels of divalproex (total bedtime dose) and divalproex ER (1:1) were highly correlated at a.m. (12-hour after last dose). However, divalproex ER yielded a sustained VPA level at p.m. trough (24-hr after last dose) compared to divalproex total dose qhs ($p<0.001$). There were no significant differences in VPA levels for divalproex ER (1:1) versus higher dosed divalproex ER (1:1+500mg). Baseline Young Mania Rating Scale (5.83 ±4.71); Hamilton Rating Scale for Depression (5.33 ±3.61); and Clinical Global Impression Scale (2.67 ±0.82) did not significantly change during the study. Divalproex ER was well tolerated.

Conclusion: As predicted, the switch from divalproex to divalproex ER in stable patients with bipolar disorder was well tolerated, maintained stability of symptoms, and resulted in consistent VPA levels throughout the day.

Source of Funding: Abbott Laboratories.

Session I – 111

Bioavailability of Two Long-Acting Formulations of Methylphenidate

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The objectives of the present study were to compare the rate and extent of absorption of methylphenidate (MPH) in Ritalin®LA (20 mg) and Concerta® (18 mg) formulations utilized in the treatment of attention-deficit hyperactivity disorder (ADHD). Nineteen healthy subjects (10 male/9 female), aged 21-34 completed this two-way-crossover-study. On Day 1 subjects randomly received Ritalin®LA 20 mg or Concerta®18 mg (manufacturer recommended starting dose). On Day 8 subjects received the alternate treatment. A total of 19 plasma samples, per patient, per treatment, were collected over 24 hours to determine MPH plasma concentrations, and to compare the rate and extent of absorption. The mean $C_{max(0-4)}$ and $AUC_{(0-4)}$ of the two treatments were compared in the context of an analysis of variance model (ANOVA) for a 2x2 crossover design. The relative bioavailability in terms of $AUC_{(0-inf)}$ between the formulations was assessed using a 90% confidence interval. All AUC and C_{max} variables were analyzed separately, with log-transformation. Ritalin® LA displayed a biphasic PK profile over a 24 hour period. Concerta® demonstrated an ascending PK profile. Ritalin®LA exhibited a more rapid rise in plasma concentration, and higher peak concentrations throughout most of the absorption curves compared to Concerta®. Mean peak plasma concentration for the first 4 hours post-dose of Ritalin®LA was reached on average at 2.1 hours post-dosing and was approximately twice that of Concerta® (6.99 ng/ml versus 3.35 ng/ml, respectively, $p<0.001$), as was the mean $AUC_{(0-4)}$ (18.5 ng*hr/ml versus 9.33 ng*hr/ml, $p<0.001$).The second mean peak plasma concentration of Ritalin®LA, observed on average at 5.6 hours post-dosingwas 9.88 ng/ml compared to 5.87 ng/ml for Concerta® ($p<0.001$). The mean peak plasma concentrations of Concerta® reached 5.92 ng/ml at Hour 6. The 90% confidence interval of $AUC_{(0-inf)}$ mean ratio of Concerta® over Ritalin®LA was (0.80, 0.96). These results indicate that the recommended starting dose of Ritalin®LA provides a more rapid rate of absorption phase and earlier initial C_{max} than the recommended starting dose of Concerta®.

Source of Funding: Novartis Pharmaceuticals Corporation

Acknowledgments: Fred Brill, NMS, Melissa Drelich

Session I – 112

Dose Proportionality of 20, 40, and 60 mg of an Extended-Release Formulation of Mixed Amphetamine Salts in Adults

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Objective: To evaluate the dose proportionality of d- and l-amphetamine following single, oral doses of 20, 40, or 60 mg of an extended-release formulation of mixed amphetamine salts in healthy adults.

Method: Adult volunteers (N=12) were randomized to receive 20 mg (2 x 10 mg capsules), 40 mg (2 x 20 mg capsules), or 60 mg (2 x 30 mg capsules) of an extended-release formulation of mixed amphetamine salts in a 3-way crossover study design. Blood samples were taken from each subject before the dose and hourly up to 12 hours postdose, and at 14, 16, 24, 36, 48, and 60 hours postdose. Plasma d- and l-amphetamine were assayed using a validated LC/MS/MS method.

Results: The $AUC_{0-\infty}$ values (mean ± SD) for d-amphetamine were 615.7 ± 173.2, 1270.2 ± 220.8, and 1974.1 ± 458.1 ng•hr/mL for the 20, 40, and 60 mg doses, respectively. The corresponding mean C_{max} values were 32.73 ± 5.88, 67.94 ± 10.27, 106.52 ± 20.18 ng/mL. Mean $AUC_{0-\infty}$ and C_{max} values for l-amphetamine were also dose proportional.

Conclusion: Exposure to d- and l-amphetamine as quantified by PK values $AUC_{0-\infty}$ and C_{max} was linear and directly related to the quantity of drug administered following a single, oral dose of Adderall XR 20, 40, or 60 mg. Time course of drug absorption and elimination were not influenced by dose.

Source of Funding: Supported by Shire Pharmaceutical Development Inc.

Session I – 113

The Effect of Risperidone Treatment on Paroxetine-Induced Hormone Release in Drug-Free Schizophrenia and its Relationship to Clinical Improvement

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Background: There is increasing evidence that the disturbances of serotonin function may be involved in the pathophysiology of schizophrenia and that serotonin antagonists have a potiential role in the treatment of the illness. Using a neuroendocrine strategy, the present study was to investigate whether risperidone treatment would block neuroendocrine responses induced by the special serotonin reuptake inhibitor (SSRI) paroxetine and whether clinical response to risperidone is related to its serotonergic antagonism.

Methods: Forty-one inpatients (30 men and 11 women) with a diagnosis of chronic schizophrenia (DSM-III-R) were treated with a fixed dose of risperidone 6mg/day for 12 weeks after a 2-week washout period. All patients were challenged with paroxetine (40mg orally) before and after risperidone treatment, as compared with 20 age- and sex-matched normal controls. Cortisol and prolactin serum levels were measured every one hour up to 6 hours after challenge. PANSS was rated at the time of challenge tests in patients before and after risperidone treatment.

Results: Risperidone treatment produced a significant reduction of cortisol response to paroxetine challenge. Change in symptom ratings correlated significantly with reduction in cortisol response to paroxetine challenge. Moreover, better responders to risperidone treatment had significantly greater paroxetine-induced cortisol responses at baseline.

Conclusion: These results suggest that risperidone is a potent functional serotonin antagonist and this serotonin antagonism may be related to risperidone's therapeutic effects.

Source of Funding: Beijing Scientific and Technological New Stars Fund

Session I – 114

Atypical Antipsychotics Attenuate the Neurotoxicity of H_2O_2 and Aβ in PC12 Cells

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Background: Neuronal atrophy and/or cell death occurs during the course of normal aging and is accelerated during neurodegenerative diseases such as Alzheimer's disease. Oxidative stress, which causes oxidation of biologic targets, results in cell death from apoptosis and necrosis depending on the flux and the time of exposure. Clinical studies have demonstrated that atypical antipsychotics such as quetiapine and olanzapine are safe and effective in the treatment of patients with Alzheimer's disease who have behavioral disturbances and psychotic symptoms.

Methods: We investigated the ability of quetiapine and olanzapine to prevent H_2O_2- and Aβ (25-35)–induced cell death in PC12 cells. Cell viability was measured using the MTT reduction assay.

Results: After exposure to increasing concentrations of H_2O_2 (100, 200, and 400 μM), or Aβ (25-35) (1, 10, and 25 μM), cell viability decreased. Pretreatment with quetiapine and olanzapine attenuated the decrease in cell viability accordingly.

Conclusion: Our data suggest that these atypical antipsychotics may have neuroprotective potential to slow down the process of neurodegeneration in patients with Alzheimer's disease or other neurodegenerative disorders.

Source of Funding: The research presented was supported by Canadian Institutes of Health Research, Alzheimer Society of Canada, and AstraZeneca Pharmaceuticals, L.P.

Session I – 115

PPI-1019 Is an Aβ Aggregation Inhibitor and Enhances Aβ Clearance into CSF

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Objectives: To assess the effect of PPI-1019 on inhibition of Aβ aggregation and associated cytotoxicity in NT2 cells and Aβ clearance via CSF after administration to rodents.

Methods: PPI-1019 was incubated with monomeric Aβ (1-40) with or without fibrillar seed and fibril formation was monitored at various time points. Aliquots of incubation mixture, without fibrillar seed, were applied to NT2 cells to evaluate cytotoxic potential. PPI-1019 was administered intravenously to Guinea pigs (once at 0.1-10 mg/kg) and APP/PS1 mice (daily for 15 weeks at 10-15 mg/kg). Aβ was quantitated from CSF by ELISA.

Results: Sub-molar equivalents of PPI-1019 delayed the onset of fibril formation and inhibited fibril-extension in the presence of Aβ fibrillar seed. Inhibition of fibril formation was associated with attenuated cytotoxicity. CSF Aβ clearance was demonstrated in guinea pigs and APP/PS1 mice after acute or chronic administration of PPI-1019.

Conclusion: PPI-1019 may assist in clearance of Aβ from brain into CSF. This hypothesis is consistent with the inhibition of fibrillogenesis associated with PPI-1019.

Source of Funding Praedis Pharmaceuticals Incorporated.

Session I – 116

Single Dose Escalation Study of PPI-1019, an Aβ Aggregation Inhibitor

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Objectives: To assess safety, tolerability and pharmacokinetics of PPI-1019 after a single intravenous infusion in healthy male subjects.

Methods: A double-blind, placebo-controlled, inpatient and outpatient, dose escalation study was performed. Doses from 5μg/kg to 250μg/kg were administered using infusion durations of 15, 5 or 1 min. The minimum intolerated dose (MID) for each duration was based on AEs, or if a dose achieved C_{max} >1000 ng/mL. The dose level immediately below the MID defined the maximum tolerated dose (MTD). CSF samples from selected cohorts were analyzed for PPI-1019 and Aβ levels.

Results: 68 subjects completed the study. The MID_{15} (250μg/kg) was due to asymptomatic transiently and reversibly increased transaminases; MID_5 (100 μg/kg) was due to C_{max} >1000 ng/mL. Therefore MTD_{15} was 100μg/kg; MTD_5 was 50μg/kg. MTD_1 is still being determined, but based on C_{max} is likely 50μg/kg. Within a 15, 5, or 1 min regimen, dose proportionality of C_{max} and AUC were observed. A shorter duration infusion of a given dose yielded a higher C_{max}. CSF samples from 10 subjects receiving 50μg/kg were compared to 4 receiving placebo. $Aβ_{1-40}$ and PPI-1019 were detected in all evaluable CSF samples. For PPI-1019 treated subjects, CSF $Aβ_{1-40}$ from pre-dose to 12 h post dose showed a mean increase of 21%, vs. a 9% decrease among placebo subjects (p=0.19). The mean absolute increase for PPI-1019 subjects in CSF $Aβ_{1-40}$ was +0.45 nM (SD=0.88) vs. -0.22 nM (SD=0.59) decrease for placebo (p=0.19). The most frequent AEs were lightheadedness, asymptomatic transiently and reversibly increased transaminases, headache and increased pulse.

Conclusion: PPI-1019 was safe and well tolerated. PPI-1019 was detected in plasma and CSF. PPI-1019 dosing was associated with increased Aβ levels in CSF, suggesting that PPI-1019 may enhance clearance of Aβ from brain into CSF. Further testing of PPI-1019 in patients with Alzheimer's disease is warranted.

Source of Funding: Praecis Pharmaceuticals Incorporated.

Session I – 117

Dose Response Analysis of First- and Second-Generation Antipsychotics

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Introduction: It is important to determine the lowest dose of antipsychotic necessary to achieve maximal clinical benefit because: 1) exceedingly high doses will cause unnecessary side effects; and 2) treatment endpoint is variable since antipsychotic drugs rarely restore patients to complete normality but rather reduce schizophrenic symptoms. We performed an analysis of efficacy dose-response curves in order to determine the therapeutic dose range for first- and second-generation antipsychotics.

Method: We review evidence from randomized, double-blind studies that compared two or more doses of an antipsychotic in order to calculate the dose-response curve for each first-generation (FGA) or second-generation (SGA) antipsychotic and for FGAs as a group based on dose-equivalence. We identified the threshold dose, i.e., the minimal dose necessary to produce full efficacy for each drug.

Since it has been suggested that SGAs may appear more efficacious than FGAs because studies using high doses of haloperidol comparator resulted in reduced haloperidol efficacy, we evaluated the effect of haloperidol dose on efficacy difference between FGAs and SGAs.

Conclusion: In randomized fixed-dose studies of SGAs the threshold daily dose to achieve efficacy for olanzapine may be greater than 16 mg, for risperidone it is ≥ 4 mg, and for ziprasidone it is ≥120 mg. Risperidone at 2 mg/day is 50% less efficacious than higher doses. Olanzapine at about 6 mg/day is approximately 33% less effective than higher doses. Daily doses of clozapine above 400 mg are necessary for optimal treatment for many patients, particularly for acute patients.

Our findings did not show that higher doses of first-generation drugs were less efficacious than lower doses. Haloperidol dose (or all first-generation comparator converted to equivalent doses) did not affect differential efficacy of second- versus first-generation antipsychotics by drug or in a two-way ANOVA model with second-generation effectiveness as a second factor.

Source of Funding: Academic institutional support

Session I – 118

The Impact of Galantamine on the Incidence of Behavioral Disturbances in Patients with Dementia

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Background: Approximately 80% of patients with dementia exhibit behavioral and psychological symptoms during the course of the disease that are associated with caregiver distress and drive the need for institutional care. Whereas the benefit of acetylcholinesterase inhibitor (AChEI) treatment in Alzheimer's disease (AD) has been previously reported, the efficacy of AChEIs on behavior in vascular dementia (VaD) and AD with cerebrovascular disease (AD + CVD) has not been characterized. Galantamine, a novel cholinomimetic agent, has a dual mechanism of action: inhibiting acetylcholinesterase and modulating nicotinic receptors. This study evaluated the effect of galantamine on the behavioral symptoms in mild-to-moderate VaD or AD + CVD.

Methods: A multicenter, double-blind, placebo-controlled, 6-month trial was undertaken in Europe and Canada. After a 4-week, single-blind, placebo run-in period, patients were randomized to placebo or galantamine 24 mg/day. Behavioral changes were assessed using the Neuropsychiatric Inventory (NPI). Mean changes in 10 NPI items compared with baseline levels are reported. Adverse events (AEs) were monitored.

Results: At 6 months, galantamine was associated with a 1.2- (SE: 0.6) point improvement on the NPI total score compared with a 1.0- (0.9) point deterioration in the placebo group (difference 2.2 points, $p = 0.0164$). Galantamine was superior to placebo on all NPI items except agitation/aggression and depression/dysphoria, with a statistically significant benefit for anxiety, apathy/indifference, and delusions ($p < 0.05$). In the VaD and AD + CVD subgroups, galantamine was superior to placebo on all but 3 (depression/dysphoria, hallucinations, irritability/lability) and 4 (agitation/aggression, depression/dysphoria, disinhibition, elation/euphoria) items, respectively. AEs from galantamine were mainly gastrointestinal, of mild-to-moderate severity, and confined to the dose-escalation period.

Conclusions: Galantamine delays the emergence of behavioral symptoms in patients with VaD or AD + CVD. Delaying behavioral symptoms may enhance quality of life, ease caregiver burden, and postpone/prevent admission to long-term care facilities.

Source of Funding: Janssen Pharmaceutica Products, L.P.

Session I – 119

Safety and Tolerability of Memantine in the Treatment of Patients With Vascular Dementia

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Background: Memantine, a moderate affinity, uncompetitive NMDA receptor antagonist, has been shown in several multicenter, double-blind, placebo-controlled trials to be effective and safe for use in the treatment of dementia of various stages and etiologies, including Alzheimer's disease (AD) and vascular dementia (VaD). Memantine is approved in Europe and is under investigation in the US for the treatment of AD. There are currently no therapeutic agents indicated for VaD.

Methods: Data from two similarly designed double-blind, placebo-controlled trials were pooled to analyze the safety and tolerability of memantine in patients diagnosed with mild to moderate VaD (based on NINDS-AIREN criteria). Memantine treatment began at a dose of 5 mg/day once daily, was increased by 5 mg weekly and was maintained at the target dose of 20 mg/day (10 mg twice daily) for 28 weeks. Safety was assessed by monitoring adverse events (AEs), vital signs, and laboratory tests.

Results: Included in these analyses and treated for a mean duration of 170 days were 442 placebo- and 460 memantine-treated patients (mean age 77 years). The percentage of patients who prematurely discontinued was similar in placebo (22%) and memantine (23%) groups. The most common reason for discontinuation was AEs (11% placebo, 13% memantine), with similar AE profiles for both groups. In both groups 74% of patients reported at least one AE. Only dizziness, constipation, and headache were reported in >5% of memantine patients at an incidence rate higher than placebo. There were no clinically important changes in vital signs or laboratory parameters from baseline to endpoint. The percentage of patients with vital signs or laboratory parameters of potential clinical significance was small, with no noteworthy differences between memantine and placebo groups.

Conclusions: Therefore, in pooled analyses, 20 mg/day memantine demonstrated a safety profile similar to that of placebo and was shown to be well-tolerated and safe in the treatment of patients with vascular dementia.

Source of Funding: Supported by Forest Laboratories, Inc. and Merz Pharmaceuticals GmbH

Session I – 120

Psychosocial Impairment Associated with an Arrest History Among People with Bipolar Disorder

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Objective: To assess psychosocial impairment associated with a prior arrest or incarceration among people with bipolar disorder (BPD) in the U.S.

Methods: 3059 subjects from a general population epidemiologic study of BPD were mailed a follow-up survey containing: Mood Disorders Questionnaire (MDQ), Social Adjustment Scale, and questions regarding work and prior arrest history (PAH).

Results: There was an 80% response rate to the survey and 1167 screened positive for BPD using the MDQ. MDQ+ subjects with a PAH were more likely to be male ($p<.0001$) and have lower income ($p<.011$). Demographics were controlled for in the analysis. 1141 completed the PAH question with 222 reporting "prior history of arrest or jail other than drunk driving". Compared to no PAH, those with PAH were more likely ($p<.01$) to endorse MDQ items "excessive, foolish or risky behavior" and "spending money caused problems", report greater psychosocial impairment ($p<.001$); report a prior job loss ($p<.001$) and report problems with alcohol/drug use ($p<.001$). BPD diagnosis is roughly the same for both groups but those with PAH were more likely to use mood stabilizers ($p<.01$).

Conclusions: Arrest history among those with BPD is associated with significantly greater psychosocial impairment and drug abuse.

This research was supported by a grant from GlaxoSmithKline

Session II – 1

Concomitant Use of Valproate and Lamotrigine in Bipolar I Disorder

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Background: Valproate reduces lamotrigine clearance, thereby increasing serum concentrations and leading to potential safety concerns. We evaluated the tolerability of concomitant lamotrigine and valproate treatment in bipolar I disorder.

Methods: Data from the preliminary phase of two large prophylaxis trials (GW 2003 and 2006) of bipolar I disorder were pooled. Lamotrigine dose was reduced to half the recommended titration rate for patients receiving valproate. Psychiatric rating scale scores and adverse events were examined.

Results: 200 patients received concomitant lamotrigine and valproate therapy; the majority of patients receiving at least 7 weeks of co-exposure. Mean CGI-S and GAS scores were respectively 4.4 (SD 0.7) and 48.8 (SD 9.6) at study entry and 2.9 (SD 1.3) and 66.7 (SD 17.1) at the end of the preliminary phase. The most common adverse events were headache (29%), infection (17%), nausea (15%) and rash (14%). No cases of serious rash were reported. No significant difference in rash was observed between patients who received concomitant therapy and those who did not (14% vs. 10%, p=0.22).

Conclusion: Concomitant administration of lamotrigine and valproate, using recommended reductions in the titration schedule of lamotrigine, was well tolerated in patients with bipolar I disorder.

Source of Funding: GlaxoSmithKline

Session II – 2

Health Resource Utilization in Bipolar Depression Compared to Unipolar Depression and Healthy Controls

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Objective: To examine the patterns of health resource utilization in bipolar depression (BP-D), unipolar depression (UP-D), and healthy controls.

Methods: A self-administered survey was completed by a sample of subjects who had previously participated in a general population survey. Subjects who screened positive for bipolar disorder (MDQ+) or reported a diagnosis of bipolar disorder and depression were considered BP-D (n=395). The UP-D (n=794) group reported a diagnosis of depression, were MDQ-, and did not report a diagnosis of bipolar disorder. The healthy control group (n=1612) consisted of those reporting no psychiatric conditions. Results were adjusted for demographic differences among groups.

Results: Depression severity was significantly ($p<0.01$) worse in BP-D vs UP-D. Compared to UP-D subjects, BP-D subjects consulted a healthcare provider earlier (age 25 versus 33, $p<.001$), were more likely to report a psychiatrist or psychologist consult, psychiatric hospital admission, PC visit, ER/urgent care use and social service use ($p<0.01$ for all). Those with BP-D were also more likely to report drug or alcohol abuse ($p<0.01$) and other co-morbid psychiatric conditions (anxiety, panic, eating disorder, all $p<0.01$).

Conclusions: BP-D is associated with more severe depression, medical comorbidities, and emergency/urgent care use than UP-D or healthy controls.

Source of Funding: GlaxoSmithKline

Session II – 3

Rehospitalization Rates of Patients with Bipolar Disorder Discharged on a Mood Stabilizer Versus a Mood Stabilizer Plus an Atypical Antipsychotic

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Background: Atypical antipsychotics improve symptoms of bipolar disorder and patient outcomes. Evaluation of rehospitalization rates is one method of assessing outcome in patients with bipolar disorder. This study examined one-year rehospitalization rates of patients with bipolar disorder discharged on a mood stabilizer alone versus a mood stabilizer plus typical or atypical antipsychotic.

Methods: Patients with bipolar disorder discharged from a state psychiatric hospital while taking a mood stabilizer alone (N=157), a mood stabilizer plus a typical antipsychotic (N=84), or a mood stabilizer plus an atypical antipsychotic (N=238) between August 1, 1997, and June 30, 2000, were considered for the study. One-year rehospitalization rates were examined from August 1, 1997, to June 30, 2001. Time to rehospitalization was measured by the Kaplan-Meier formula. The Cox proportional hazards regression model was used to analyze covariates thought to affect time to rehospitalization.

Results: 23% of patients on a mood stabilizer alone, 27% on a mood stabilizer plus a typical antipsychotic, and 25% on a mood stabilizer plus an atypical antipsychotic (olanzapine or risperidone) were rehospitalized within one year after discharge. No significant differences existed in rehospitalization rate or time to rehospitalization between groups. Previous hospitalizations were greater in the combination treatment groups, and prior psychiatric hospitalizations contributed to the risk of readmission. After adjusting for previous hospitalizations, there were no differences in rehospitalization rates. The combination treatment groups contained more patients in the manic stage, more patients with psychotic symptoms, and had a longer length of hospitalization than mood stabilizer monotherapy.

Conclusions: No differences occurred in rehospitalization rates between patients discharged on a mood stabilizer alone, a mood stabilizer plus a typical antipsychotic, or a mood stabilizer plus an atypical antipsychotic. There was no difference in rehospitalization rates between patients discharged on a mood stabilizer plus olanzapine or risperidone. The number of previous psychiatric hospitalizations was a predictor of rehospitalization. Mood stabilizer and antipsychotic combination treatment appeared to be used in a more severely ill patient population.

Source of Funding: Supported in part by grants from Eli Lilly and Company and the Texas Department of Mental Health and Mental Retardation

Session II – 4

Can Bipolar Depression Be Treated Without Destabilizing Mood?

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Objective: To assess whether randomized clinical trials of lamotrigine provide evidence for or against exacerbation of mania in bipolar I patients.

Methods: Data from 8 controlled clinical trials (lamotrigine=827, placebo=685) and two 18-month prophylaxis trials (lamotrigine=227, placebo=190) were analyzed. Lamotrigine treatment ranged from 3 weeks to 18 months, as adjunctive or monotherapy, at daily doses of 50-500 mg.

Results: In the controlled trials, lamotrigine was not associated with an increased risk of manic/hypomanic/mixed episodes reported as adverse events (5% lamotrigine, 4% placebo), serious adverse events (3% lamotrigine, 3% placebo), or adverse events leading to discontinuation (2% lamotrigine, 1% placebo). In prophylaxis trials, 21% of lamotrigine-treated patients had an adverse event of mania or required intervention for mania in the randomized phase compared with placebo (26%). Time to intervention for mania was longer for lamotrigine compared with placebo. Mania Rating Scale (MRS) mean scores at randomization and at the end of the treatment period were similar between lamotrigine and placebo. The percentage of patients with a MRS score >10 at any time after randomization was 15% for lamotrigine and 12% for placebo.

Conclusions: Data from multiple clinical trials indicate that lamotrigine does not exacerbate mania when used to treat bipolar depression.

Source of Funding: GlaxoSmithKline

Session II – 5

Quetiapine as Monotherapy for Mania Associated with Bipolar Disorder

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Objective: To evaluate the efficacy and safety of quetiapine (Seroquel®) monotherapy for the treatment of bipolar mania in a large cohort of patients.

Method: 604 patients (bipolar I disorder, manic episode) were randomized to 12 weeks, double-blind, placebo-controlled treatment with quetiapine (QTP, up to 800 mg/d). Standard agents (lithium or haloperidol) were used as controls to assess assay sensitivity.

Results: 60.8% (127/209) of QTP- vs 38.9% (77/198) of PBO-treated patients completed the trial. A statistically significant improvement in YMRS total score was observed from Day 4 onward in the QTP group vs PBO (P=0.021). The change from baseline in YMRS score at Day 21 (the primary efficacy endpoint) was –13.58 for quetiapine vs –7.76 for placebo (P<0.0001); the difference in favor of quetiapine increased by Day 84 (P<0.0001). Significantly more QTP-treated patients achieved a YMRS response (≥50% decrease from baseline) at Day 21 (QTP 48.1%; PBO 31.3%; P=0.0006). The YMRS scores of patients in the lithium and haloperidol groups also improved significantly compared to placebo. Common adverse events (≥10%) in the quetiapine group were somnolence, dry mouth, and insomnia (insomnia was similar in all groups, including placebo). Tremor was common only in the haloperidol and lithium groups. Akathisia and extrapyramidal syndrome were common in the haloperidol group only. Mean last-week quetiapine dose in responders at Day 21 was 575.5 mg/d.

Conclusions: Quetiapine monotherapy is effective, fast acting, and well tolerated in the treatment of mania.

Source of Funding: AstraZeneca

Session II – 6

Symptomatic Response to Treatment in Bipolar I Disorder

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Background: To examine the longitudinal effect of lamotrigine, lithium, and placebo on affective symptoms of bipolar I disorder.

Methods: Lamotrigine was initiated during an 8- to 16-week open-label phase while other psychotropic drugs were discontinued in currently or recently depressed bipolar I patients. Patients meeting stability criteria (CGI-I < 3) were randomized to lamotrigine (50mg, 200mg or 400mg daily), lithium (0.8 to 1.1mEq/L), or placebo for up to 18 months double-blind treatment. Symptom intensity ratings of depression (HAM-D), mood elevation (YMRS) and overall illness severity (CGI) were examined using repeated measures, last observation carried forward, and random effects mixed model analyses.

Results: After initial stabilization, the average and visit-wise change in depressive symptoms was more favorable in the lamotrigine group compared with placebo (2.5 vs. 4.9 average HAM-D change, respectively; $p=0.002$). Conversely, lithium was superior to placebo in preventing the return of manic symptoms without worsening depressive symptoms in the visit-wise analysis ($p<0.05$). Lamotrigine did not lead to worsening of manic symptoms.

Conclusions: Lamotrigine and lithium appear to have distinct and potentially complementary effects on affective symptoms in bipolar I patients.

Source of Funding: GlaxoSmithKline

Session II – 7

Determinants and Consequences of Dose Changes in a Flexible Dose Study

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Introduction: Flexible dose studies allow the dose to be adjusted during the course of the treatment and contain useful information on the condition of patients preceding and following dose changes. In the present analysis we identify factors that predict dose changes during a flexible dose study, and determine whether dose changes predict changes in efficacy and side effects.

Methods: Data from a 12-week, double-blind, flexible-dose study in patients with acute mania randomized to receive olanzapine (OLZ) (5-20 mg/d, N=234) or haloperidol (HAL) (3-15 mg/d, N=219) were analyzed *post hoc*. Associations between dose changes and efficacy, extrapyramidal symptoms (EPS), weight changes (as measured by changes in Body Mass Index), and unsolicited EPS related adverse events (EPSAEs) were modeled using repeated measures analyses.

Results: For both therapies, baseline illness severity as well as level of efficacy achieved, EPS scales, and severity of EPSAEs experienced during the previous week predicted dose changes. Patients whose dose was decreased showed less improvement on subsequent visits (p=.02 for OLZ, and p=0.002 for HAL). The direction of change in EPS scales followed the direction of change in dose of HAL, but these changes were not predicted by dose changes of OLZ. Weight change was not predicted by dose change.

Conclusions: Efficacy and tolerability are predictive of antipsychotic dose adjustments. For both treatments dose changes affect efficacy. For HAL, EPS were influenced by change in dose. For OLZ, overall EPS rates were lower and were not affected by dose changes, which may allow for more aggressive dosing to increase therapeutic benefit.

Source of Funding: Eli Lilly and Company

Session II – 8

Relation of Antidepressants to Mood Patterns in Patients with Bipolar Disorder

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Objective: Although antidepressants are widely prescribed for patients with bipolar disorder, the risk for inducing mania or rapid cycling remains unclear. This study compared mood patterns in patients with bipolar disorder who were either taking or not taking antidepressants.

Method: 80 patients with bipolar disorder (I or II) recorded mood, sleep, medications and life events daily for 3 months into self-reporting software (ChronoRecord). 5119 days of data from 47 patients taking antidepressants and 3543 days of data from 33 patients not taking antidepressants were received. Data was analyzed both by group and individual. There were no statistically significant demographic differences between the groups.

Results: For all days, patients taking antidepressants were depressed 29% of days, normal for 65.1% of days and manic for 6.0% of days. Patients not taking antidepressants were depressed 13.8% of days, normal for 76.0% of days and manic for 10.2% of days ($p<.001$). In both groups, 2/3 of all mood changes for a lag of 1-3 days were small, between -5 to 5 on a 100-point scale. Mood switches between depression and mania were rare with no statistical difference in frequency between those not taking antidepressants (0.7%) or taking antidepressants (0.9%). There was no statistical difference between the groups in the frequency of large mood changes (>10 on a 100-point scale).

Conclusions: The primary difference observed between patients taking or not taking antidepressants was the time spent in depressed or normal mood. Patients taking antidepressants were depressed twice as often and appear to have a downshift in baseline mood. From their respective baseline mood, the frequency and size of mood changes was similar in both groups.

Source of Funding: UCLA Department of Psychiatry

Session II – 9

Effect of Antidepressant Use on Admissions to Hospital Among Elderly Bipolar Patients

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Background: There have been no studies of the use of antidepressant medications in elderly bipolar patients. The goal of this study was to evaluate the effect of antidepressant use on hospitalization rates for depression and mania among elderly bipolar patients.

Methods: Retrospective cohort design with data obtained from the administrative databases of the Province of Ontario, Canada maintained at the Institute for Clinical Evaluative Studies. The information held in these databases includes all admissions to hospital (with discharge diagnosis) in the Province of Ontario, and all prescriptions paid for by the Province (>95% of prescriptions to elderly patients). This information is linked to demographic and health care utilization data on each elderly patient. The eligible patients for this study were all residents of the Province of Ontario who were >65 years old and had a past admission for mania or bipolar depression. The cohort was defined as eligible subjects who received a prescription for an antidepressant between 1994 and 2001 and exposure continued as long as repeat prescriptions were filled within 90 days. Control subjects were eligible patients who did not receive an antidepressant between 1994 and 2001.

Results: The study identified 8,109 eligible subjects. The cohort included 910 subjects who were prescribed an antidepressant medication. Rates of admission to hospital for both mania and bipolar depression were significantly lower among the cohort group as compared to the control group. In the year prior to receiving the antidepressant, cohort subjects had greater health care utilization than control subjects did.

Conclusion: Elderly bipolar subjects who were treated with an antidepressant had a decreased rate of hospitalization for both bipolar depression and mania as compared to elderly bipolar subjects not receiving an antidepressant. The results of this study may have major implications for the treatment of elderly bipolar patients. However, interpretation is limited by the retrospective design.

Source of Funding: No external funding

Session II – 10

The Effects of Mood Stabilizing Medication on Neuronal Activation During Performance of a Working Memory Task in Patients with Bipolar Disorder

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Background: Bipolar disorder is a serious psychiatric illness that affects ~1.5% of the population and is a major source of individual morbidity and societal cost. Evidence suggests that bipolar disorder is associated with cognitive deficits involving working memory that may persist with resolution of mood symptoms and play an important role in the morbidity of the illness. Using fMRI, we have previously demonstrated significant changes in neuronal activation in bipolar patients during performance of a working memory task. Compared to healthy controls, bipolar patients demonstrated significantly greater activation in regions including the dorsolateral prefrontal cortex (DLPFC), posterior and temporal cortex, and subcortical structures. In this study, we compared functional activation in unmedicated patients with that of patients receiving psychotropic medication.

Methods: Five unmedicated patients with bipolar disorder were compared with a matched group of patients receiving therapeutic doses of mood stabilizing medications. Subjects were matched for age, education and illness severity. Subjects performed a zero-back attention task and a two-back working memory task in a boxcar design during fMRI; the zero-back task served as the contrast condition for the two-back task. Performance was calculated using discriminability and reaction time. Neuronal activation was determined using voxel-by-voxel comparisons across condition. Voxel-by-voxel t-statistics were used to create individual statistical maps. All scans were normalized to Talairach space for examination of composite data. Unmedicated and medicated cohorts were compared by on a voxel-by-voxel basis utilizing a Mann-Whitney comparison.

Results: Unmedicated and medicated bipolar patients did not significantly differ in performance on zero- and two-back tasks. While no significant differences were observed in regional activation, we found differences in degree of activation between patient groups, of moderate effect size. Unmedicated patients demonstrated increased activation in several regions, distributed across the working memory network. Regions included DLPFC, posterior parietal cortex, and subcortical structures.

Conclusions: Our data suggest that mood-stabilizing medications diffusely decrease neuronal activation in bipolar patients during working memory task performance. While not reaching significance, the medicated bipolar patients demonstrated a moderate decrease in activation across the working memory "network." These findings suggest that mood-stabilizing medications may act at least partially by inhibiting increases in neuronal activation observed in bipolar patients, leading to a partial "renormalization" of activation patterns.

Source of Funding: This study was funded as part of a grant from the Stanley Medical Research Institute

Session II – 11

A 3-Week Double-Blind Placebo-Controlled Study of Extended Release Carbamazepine in the Treatment of Acute Mania in Bipolar Disorder

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Objective: Carbamazepine (CBZ) is a frequently prescribed therapy for bipolar disorder, but most controlled evaluations of CBZ have been small or confounded by concomitant therapy, and all have used conventional, immediate-release CBZ formulations. A 3-week double-blind placebo-controlled study and a 6-month open extension were carried out to assess the efficacy of carbamazepine extended-release capsules (CBZ-ERC; Carbatrol®) given as monotherapy in patients with bipolar disorder.

Methods: 204 patients diagnosed with manic or mixed bipolar disorder received either CBZ-ERC or placebo BID for 3 weeks following a 7-day single-blind placebo lead-in period and were hospitalized through at least the first 7 days of double-blind treatment. Lorazepam was allowed for the first 2 weeks of the study, but other psyhotropic medications were prohibited. CBZ-ERC dose was initiated at 400 mg/day and could be increased up to 1600 mg/day. Weekly efficacy assessments included the Young Mania Rating Scale (YMRS), and the Clinical Global Impression (CGI) scale. 92 patients who participated in this or another 3-week study continued to receive open-label CBZ-ERC and were evaluated for up to 6 months.

Results: 96/204 (47.1%) patients completed the 3-week study. Discontinuation rates were similar between treatment groups. Compared to placebo, treatment with CBZ-ERC led to significantly greater improvements in YMRS and CGI at 14 days and 21 days. At the end point of the 3-week study, YMRS total score had decreased at least 50% in 41.5% of CBZ-ERC–treated patients and 22.4% of placebo-treated patients. Efficacy improvements in CBZ-ERC-treated patients were maintained during the 6 month open extension, and previously treated placebo patients, when transferred to CBZ-ERC, showed significant improvements by the first visit (1 month). The most common adverse events during CBZ-ERC treatment were dizziness, nausea, and somnolence. There were no significant weight increases in either study.

Conclusions: These results establish the efficacy of Carbamazepine extended-release capsules in acute mania and further validate the role of Carbamazepine as a established member of the limited number of medications available for the treatment of bipolar disorder.

Source of Funding: Shire Pharmaceutical Development Inc.

Session II – 12

Adjunctive Family Therapy and Recovery from Bipolar I Mood Episodes

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Background: Patients with acute mood episodes of bipolar I disorder often receive psychotherapy in combination with medications, but the efficacy of this practice is not known.

Methods: Acutely ill patients were assessed with the Structured Clinical Instrument for DSM-III-R – Patient Version, and enrolled if they met criteria for acute bipolar I disorder (manic, depressed, or mixed), and were living with or in regular contact with relatives or significant others. Subjects were randomly assigned to one of three treatments for 28 months: family therapy plus pharmacotherapy, multifamily psychoeducational group therapy plus pharmacotherapy, or pharmacotherapy alone. All subjects were prescribed a mood stabilizer, and other medications were used as well. Subjects were assessed monthly with the Modified Hamilton Rating Scale for Depression and the Bech-Rafaelsen Mania Scale. Recovery was defined as two consecutive months with Bech-Raphaelsen scores < 6 and Hamilton scores < 7. Duration of the acute mood episode was calculated using survival analysis.

Results: A total of 92 patients enrolled in the study. Of the 29 subjects assigned to pharmacotherapy alone, 16 (55%) recovered, as did 16 (48%) of the 33 subjects assigned to family therapy plus pharmacotherapy, and 21 (70%) of the 30 subjects assigned to multifamily psychoeducational group therapy plus pharmacotherapy ($\chi^2 = 3.08$, df = 2, p = 0.21). The median time from randomization to recovery for subjects assigned to pharmacotherapy alone was 9 months, for subjects assigned to family therapy plus pharmacotherapy was 10 months, and for subjects assigned to multifamily group therapy plus pharmacotherapy was 7 months (log-rank $\chi^2 = 2.03$, df = 2, p = 0.36).

Conclusion: Neither adjunctive family therapy nor adjunctive multifamily psychoeducational group therapy significantly improves recovery from acute mood episodes of bipolar I disorder, compared to treatment with pharmacotherapy alone.

Source of Funding: NIMH grant R01 MH48171 (principal investigator: Dr. Miller)

Session II – 13

A Double-Blind Prolongation Study of the Combined Treatment of Depression with Mirtazapine and Paroxetine

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Background: Double-blind prolongation studies examining the effect of antidepressant drugs after achieving a response in depression generally show a relapse rate of about half that of patients on placebo. However, a significant proportion of patients end up on a combination of two antidepressants to achieve response and/or remission. To our knowledge, there is no controlled data on the efficacy of two drugs used concomitantly in treatment prolongation.

Methods: Sixty-two patients with unipolar depression were randomized into a 6-week double-blind trial to receive either mirtazapine (M; 30 mg/day), paroxetine (P; 20 mg/day) or their combination (C) from Day 1. At Day 28, patients failing to respond to one drug had their daily dose increased by 50%. At Day 42, non-responders on one agent received in addition the other medication for 2 weeks, whereas combination non-responders had a 50% increase in dose of both drugs for these additional 2 weeks. The regimen that brought response was then continued for 4 months.

Results: Fifty-three patients reached Day 42 with 6/21 responding to M, 7/21 to P and 11/20 to C. After 56 days of treatment, 34 patients consented to the prolongation, although 39, or 63%, achieved remission. A total of 21 patients were treated for 180 days and remained in remission (M: 3/5; P: 2/4; C: 16/25). Two patients were lost to follow up (M, P), 1 withdrew consent (M), 6 dropped out because of side effects (C) all while being in remission, and only 4 relapsed (P: 1; C: 3).

Conclusions: Many fewer patients on a single drug were followed in this prolongation study because of the superiority of drug combination. Remission was maintained in the vast majority of patients on the combination, although side effects attenuated the completion rate in these patients.

Source of Funding: Organon

Session II – 14

Open-Label Maintenance Treatment for Bipolar Depression Using Olanzapine or Olanzapine/Fluoxetine Combination

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Background: Olanzapine/fluoxetine combination (OFC) has shown efficacy in treating bipolar depression.[1] Present analyses examined 6-month maintenance data for subjects who achieved remission of depressive symptoms following acute treatment.

Methods: 377 subjects with bipolar depression completed 8-weeks of randomized, double-blind treatment using olanzapine (OLZ, n=179), placebo (n=145), or OFC (n=55). Of these, 192 were in remission (MADRS ≤ 12) upon entering open-label treatment, at which time they were switched from their acute-phase treatment to 5-20mg/day open-label OLZ. After 1 week on OLZ, subjects could be switched to OFC as needed. Primary efficacy measure was the Montgomery-Åsberg Depression Rating Scale (MADRS). Manic symptoms were monitored using the Young Mania Rating Scale (YMRS). Time to relapse (MADRS >15) was estimated using Kaplan-Meier survival analysis.[2]

Results: Of the 192 remitters, 120 (62.5%) remained free from relapse over the 6-month open-label period. For the 72 subjects (37.5%) who relapsed, median time to relapse was 194 days. Mean MADRS total score at open-label endpoint was 7.93 (SD 9.24, n=192) using a last-observation-carried-forward (LOCF) methodology.

Conclusion: This open-label study suggests that OLZ and OFC may represent treatment options in the long-term management of bipolar depression. Further studies are necessary to replicate these findings using appropriate controls and double-blind methodology.

Source of Funding: Eli Lilly and Company

References:

1 Tohen M, Vieta E, Ketter TA, et al. Olanzapine in the treatment of bipolar depression. *The International Journal of Neuropsychopharmacology* 2002:5(Suppl 1):S109.
2 Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53 :457-481.

Session II – 15

Analysis of Treatment-Emergent Mania with Olanzapine/Fluoxetine Combination in the Treatment of Bipolar Depression

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Objective: Treatment-emergent mania is often associated with bipolar depression in patients treated with antidepressants without mood stabilizers[a,b]. This study compares treatment-emergent mania rates in bipolar depressed patients treated with olanzapine/fluoxetine combination (OFC), olanzapine, or placebo.

Methods: In this 8-week, double blind treatment, patients (n=833) with bipolar depression (baseline MADRS total scores $\geq$20) were randomized to OFC (6/25, 6/50, or 12/50 mg/day, n=86), olanzapine (5-20 mg/day, n=370), or placebo (n=377). 562 subjects also participated in an optional 6-month, open-label extension phase where olanzapine or OFC could be given at any time. Treatment-emergent mania was evaluated with the YMRS.

Results: In the acute phase, treatment-emergent mania (baseline YMRS <15 and $\geq$15 at any subsequent visit) did not differ between groups (OFC 6.4%, olanzapine 5.7%, placebo 6.7%, p=.861). Subjects on OFC (-1.38 $\pm$5.59 SD) and olanzapine (-0.55 $\pm$5.91 SD) had greater decreases in YMRS than those on placebo (0.57 $\pm$6.09 SD)(p=.027 and p<.001, respectively). In the extension phase (OFC n=404), OFC subjects' treatment-emergent mania rate was 4.7% (n=19) at anytime, and only 4.0% (n=16) of OFC patients met treatment-emergent mania criterion at endpoint. YMRS mean change from baseline (3.51 $\pm$3.69 SD) to endpoint (0.03 $\pm$5.42 SD) for OFC was not significant.

Conclusions: Neither OFC nor olanzapine had a greater risk of acute treatment-emergent mania than placebo. The rate of treatment-emergent mania for OFC was low during a 6-month, open-label extension. Data suggest OFC does not present a risk of treatment-emergent mania in bipolar depression.

Source of Funding: Eli Lilly and Company

References:

a. Goodwin FK and Jamison KR. (1990). *Manic-depressive illness*. Oxford: New York, 630-663.
b. Peet M. (1994). Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. *Br J Psychiatry*. 164:549-550.

Session II – 16

Effects of Lamotrigine and Lithium on Body Weight in Bipolar I Disorder

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Objective: To examine the effects of mood stabilizers for bipolar I disorder on body weight.

Methods: 638 patients randomized to 18 months of double-blind monotherapy with lamotrigine (n=280; 50-400mg/day fixed and flexible dose), lithium (n=167; 0.8-1.1mEq) or placebo (n=191) were grouped by pretreatment body mass index (BMI): not obese = BMI < 30, obese = BMI $\geq$ 30. Mean observed change in body weight was examined through 52 weeks of treatment. Random effects mixed model with subject as a random effect and treatment, BMI category, visit, BMI category by visit interaction, and treatment by visit interaction as fixed effects was performed.

Results: After 52 weeks of treatment, mean change in body weight was significantly lower in the lamotrigine treatment group compared with placebo ($p< 0.011$) and compared with lithium ($p<0.0001$). These differences were evident in both BMI categories, but were most evident in the obese category of patients: placebo + 1.46 kg, lithium +3.3 kg, and lamotrigine -2.96 kg.

Conclusions: Changes in body weight were correlated with choice of mood stabilizer and body mass index. Patients categorized as obese were at greatest risk for weight gain with lithium.

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Session II – 17

Patterns of Weight Gain in Bipolar Patients Treated with Olanzapine or Divalproex

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Objective: To examine weight gain and related parameters for olanzapine and divalproex sodium.

Method: This post-hoc analysis of a 47-week, double-blind, randomized clinical trial compared olanzapine (5-20 mg/day) and divalproex (500-2500 mg/day) for bipolar mania (N=251). Weight was analyzed using mean change from baseline with ANOVA and categorically using Fisher's exact test. Possible weight gain predictors were entered into ANOVAs (last observation carried forward) with all factors and their interaction with treatment.

Results: Patterns of weight gain differed between treatment groups. Olanzapine-treated patients had sharper mean increases early in treatment which plateaued later. Divalproex-treated patients had more gradual weight increases with no significant differences from olanzapine from week 19 onward. At week 47, significant effects were found for remission status (mean change 4.42 kg for remitters and 2.69 kg for non-remitters, p=.014) and interaction of age by treatment (younger olanzapine-treated patients and middle-aged divalproex-treated patients gained more weight, p=.002). Correlations between change in weight and other variables (psychiatric ratings, glucose, cholesterol, and blood pressure) were small and did not differ between groups.

Discussion: Significant weight increase occurred with both treatments, albeit patterns differed. Weight increases over 47 weeks were weakly correlated with blood pressure, non-fasting glucose or total cholesterol.

Source of Funding: Eli Lilly and Company

Session II – 18

Service Utilization Among Patients with Bipolar Disorder in the Texas Medication Algorithm Project

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Background: In the Texas Medication Algorithm Project (TMAP), outpatients with bipolar disorderreceived algorithm driven treatment and patient/family educational programs (ALGO) versus treatment as usual (TAU) for 1-2 years in Texas Department of Mental Health and Mental Retardation (MHMR) clinics. Clinical outcomes were measured in both groups by independent assessors at quarterly intervals, and have been reported elsewhere. The current report describes differences in service utilization between ALGO and TAU.

Method: Service utilization was measured from administrative files, abstracted medical records, and patient self-reports to describe over time patient frequency and duration of contacts with MHMR and non-MHMR providers.

Results: There were significant differences in utilization of outpatient MHMR services between ALGO (n=141) and TAU (n=126). After adjusting for demographic and clinical characteristics, ALGO patients attended 13.1 MD psychiatric visits per year, or were 1.5 times ($p<.001$) more likely to see an MD than TAU patients (8.2 visits). However, time per MD visit was less for ALGO (24.6 minutes) compared to TAU (34.6 minutes)($p<.001$). Also, ALGO patients made fewer non-MD visits (23.7 vs. 26.7) (NS), at significantly reduced provider time per visit (42.5 vs. 90.5) ($p<.001$). Differences in hospitalization rates for ALGO and TAU were not significant.

Conclusions: Use of an algorithm and patient education for bipolar disorder was associated with a differential pattern of contacts with outpatient providers. Specifically, ALGO patients had more contacts with MDs, but this was offset by less time spent per visit, and considerably less time spent with non-MD professionals. Implications for cost and more detailed analyses will be presented.

Source of Funding: TMAP was funded by NIMH Grant MH-53799, Robert Wood Johnson, Meadows, and Lightner-Sams Foundations, Nanny Hogan Boyd Charitable Trust, Texas Department of Mental Health and Mental Retardation, Center for Mental Health Services, Department of Veterans Affairs, Health Services Research and Development Research Career Scientist Award (RCS92-403) (TMK), Betty Jo Hay Distinguished Chair in Mental Health and the Rosewood Corporation Chair in Biomedical Science (AJR), United States Pharmacopoeia Convention, Inc., Mental Health Connections (funding from Texas State Legislature, Dallas County Hospital District and the UT Austin College of Pharmacy), and the Southwestern Drug Corporation Centennial Fellowship in Pharmacy (MLC). Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Company, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Novartis, Organon, Pfizer, Inc. and WyethAyerst Laboratories, Inc. provided unrestricted educational grants.

Session II – 19

Needs of Family Caregivers of Patients with Bipolar Illness and Schizophrenia: Preliminary Data Using the Family Assessment of Need for Service (FANS)

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Objective: We report initial data using an instrument developed to evaluate the service needs and treatment preferences of family caregivers of patients with mental illness.

Methods: The primary family caregivers of 18 patients with bipolar disorder and 20 patients with schizophrenia were administered a 74-item semi-structured interview designed to evaluate six areas of current need: information, patient services, collaboration with patient service providers, social support, stress management/self-care, future planning. They also rated preferences for future services. Caregivers of bipolar patients were members of the Mood Disorders Support Group of New York (mdsg/ny); caregivers of schizophrenia patients were recruited through their patients' participation in ambulatory care at a university-affiliated mental health clinic.

Results: Caregivers were 73.7% female (age = 52.2 + 12.8). 54.1% were married/cohabiting, 78.9% worked, 37.8% had an income below $60,000. 50.0% of caregivers were spouses and 34.2% were parents of the patient.

Needs: Scales assessing need in the areas cited above were internally consistent (alpha coefficients: .90 - .66) and were modestly intercorrelated overall. Scales identifying the highest percent of unmet needs were Information and Stress Management: 100% and 95% of Ss reported needing information about medication side effects and mood stabilizers, respectively, while 73.7% needed relief from caregiving strain, and 65.8% wanted stress reduction education. 40% of Ss wanted a more collaborative relationship with the patient's psychiatrist. Having siblings nearby was significantly correlated with fewer needs, while income and education were correlated with increased needs on 2+ scales. A significant effect for site was not found for any of the six scales, even after controlling for sociodemographic variables correlated with both site and need score.

Preferences: 89.5% of caregivers felt they would benefit from services. Specific preferences were: leadership - family-to-family (89.5%); frequency – monthly (73.5%). Caregiver-related contents, e.g., coping (94.1%) outranked patient topics, e.g., pharmacotherapy (73.5%). Groups (91.2%) or expert consultations (88.2%) for caregivers alone were preferred over modalities involving the patient: family therapy (55.9%), multiple-family-group (41.2%).

Conclusion: Preliminary findings show caregivers of the mentally ill report substantial unmet needs, are receptive to intervention, and have clearly-defined treatment preferences that should be considered in developing services.

Source of Funding: National Institute of Mental Health MH65015

Session II – 20

Clinician Beliefs and Behaviors as Modifiers of Treatment Response in Multicenter Clinical Trials

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Objective: We examined the relationship between placebo response and clinician beliefs through development (Phase One) and validation (Phase Two) of a novel measure: the Assessment of Clinician Relationships and Expectations (ACRE) scale. The central hypothesis was that clinician beliefs and behaviors, as measured by the ACRE, would have a significant relationship with patient outcome.

Methods: In Phase One, theory-based clinician items and expert-opinion-based site items were developed and evaluated in a series of steps including item sorts, expert panel reviews, qualitative pre-pilot evaluation, and pilot investigation. Pilot evaluation tested the a priori factor structure, evaluated item characteristics and scale consistency, and derived an empirically-based factor structure. Phase Two examined the correlation between ACRE scores and outcomes for clinician-patient pairs that were created using three approaches. The first assigned a patient's outcome to a single clinician. The second assigned a patient's outcome to all clinicians contacted. The third assigned a patient's outcome based on the numbers of contacts the patient had with his/her various clinicians. The relationships of ACRE total, factor, and item scores with outcome were explored at the clinician (N=100), site (N=39), and item levels.

Results: The a priori factor structure was not supported, but an empirically derived structure with four factors named Clinical Beliefs and Behaviors, Research Beliefs and Behaviors, Clinical Patient Beliefs, and Research Patient Beliefs was produced. The derived scale contained 50 items, had acceptable reliability (.85), and discriminated between sites on scale and factor totals.

In Phase Two several hypotheses were tested, but generally not supported. The association between ACRE scores and patient outcome was in the expected direction, but not significant. ACRE total score was significantly related to Hamilton depression improvement scores, but only for those patients served by clinicians with relatively high ACRE total score.

Conclusion: The four factors derived from our work are recommended as a basis for future investigations of clinician characteristics that may be associated with placebo response formation. It is hoped that additional investigations will support the validity and utility of the ACRE scale as a predictive tool.

Source of Funding: Eli Lilly & Company

Session II – 21

Development of an Instrument to Assess Female Hypoactive Sexual Desire Disorder: Preliminary Item Response Analysis Results and Next Steps

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Background: Female Hypoactive Sexual Desire Disorder (FHSDD), is characterized by a lack of interest in normal sexual relations that causes personal distress (DSM-IV). In order to address the lack of instruments specifically developed to assess this disorder, the authors developed the Sexual Interest and Desire Inventory (SIDI). The initial version of this clinician-rated scale included symptom clusters from across the spectrum of women's sexual complaints with the intent to assess the value of all potentially relevant symptoms in a treatment population before deriving the final instrument. Therefore in addition to a number of items related to desire, this preliminary version of the SIDI included items that assessed orgasm, arousal, satisfaction with their relationships, mood, fatigue and pain.

Goal: To utilize Item Response (IR) analyses to assess the usefulness of each of the items in the preliminary version of the SIDI.

Methods: Following a one-month observational screening period, 173 patients meeting DSM IV criteria for FHSDD were entered into a three-month double-blind pharmacological treatment study. SIDIs were administered monthly and at Screen for one to four months, to all patients and TESTGRAF software was used to conduct IR analyses on the resulting data set.

Results: Increased severity of FHSDD were not reflected in SIDI items related to the severity of mood (i.e. depressive), fatigue, sex-related pain, or the quality of the patient's relationship with their partner. On the other hand, scores on items related to desire, satisfaction with their *sexual* relationship, arousal, and orgasm did increase with severity of FHSDD.

Conclusions: IR analyses revealed no obvious relationship between the overall severity of FHSDD and severity or frequency of depressive symptoms, relationship issues, fatigue or desire for affection, suggesting that these symptoms did not contribute to the assessment of FHSDD and that the corresponding items should be removed from the final instrument. Conversely, the performance of the desire and arousal items appeared to show good item response properties in relation to the severity of the disorder, suggesting the revised SIDI (which will include these items) is a useful measurement tool for assessing severity of FHSDD.

Source of Funding: Boehringer-Ingelheim

Session II – 22

Escitalopram is Effective and Well Tolerated in the Treatment of Severe Depression

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Introduction: Escitalopram is the most selective SSRI antidepressant, and has been shown to be more effective than citalopram in the treatment of severe major depression.

Objectives: To determine prospectively the effect of escitalopram in the treatment of severe depression.

Methods: Patients with severe major depression (mean baseline 24-item HAMD = 30) were randomly assigned to 8 weeks of double-blind treatment with 10-20 mg/day escitalopram (N = 147) or placebo (N = 153). Efficacy assessments included MADRS (primary efficacy measure), HAMD, and CGI. Response was prospectively defined in three ways: 50% decrease in MADRS, 50% decrease in HAMD, or CGI-I ≤ 2.

Results: Overall, 82% of patients completed the trial. For LOCF analyses, escitalopram treatment led to significant ($p < 0.05$) improvement versus placebo by week 2 in HAMD scores, and by week 4 in MADRS and CGI-I scores; statistically significant improvement compared with placebo was maintained at all subsequent visits. Approximately half of escitalopram treated patients (49-52%) at endpoint (LOCF) were responders, according to each definition, and these rates were significantly superior to placebo treatment (30-38%; $p < 0.05$). Incidence of adverse events was similar to those reported previously for escitalopram treatment. Discontinuation rates due to adverse events were low (6% escitalopram, 0 placebo).

Discussion: Escitalopram treatment is an effective and well tolerated treatment of severe major depression.

Source of Funding: Supported by Forest Laboratories, Inc.

Session II – 23

Panic Symptoms in Major Depressive Disorder

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Objective: We assessed the impact of both DSM-IV panic disorder (PD) and panic symptoms (PA-sym) on antidepressant response to fluoxetine among outpatients with major depressive disorder (MDD).

Methods: We derived a measure of PA-sym at baseline (range: 0-17) from the self-rated Symptom Questionnaire (11 items) and Beck Anxiety Inventory (6 items), and defined high PA-sym scores as $\geq$8. 329 outpatients with MDD (SCID-DSM-IV criteria) who completed 8 weeks of treatment with fluoxetine (20 mg/day) were examined. Outcome variables were HAMD-17 change scores from baseline to week 8 examined as percentage change and as response, defined as a ≥50% reduction. In addition, remission was defined as a HAMD-17 score ≤7. Logistic and multiple regression analyses were performed.

Results: Mean score for PA-sym was 5.7±3.6. Fifteen (4.6%) and thirty-eight (11.6%) subjects had current and lifetime diagnosis of PD, respectively. Only 46.4% (vs.67.5%) of patients with high PA-sym scores were responders (p=.05) and 36.1% (vs.54.7%) remitted (p=ns). PA-sym scores also predicted lower percent change of HAMD-17 score (p<.05). Severity of depression did not account for the predictive value of PA-sym. Diagnosis of PD did not significantly predict depression outcome.

Conclusions: Our data suggest that panic symptoms, but non panic disorder, significantly predict a poorer antidepressant treatment outcome among outpatients with MDD.

Source of Funding: Supported in part by NIMH grant R01-MH48483 (Dr. Fava)

Session II – 24

Sequenced Treatment Alternatives to Relieve Depression (STAR*D): A Randomized Controlled Trial in Clinical Practices - Proof of Concept

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Background: Classic efficacy trials are conducted in research clinics with symptomatic volunteers are typically recruited through media advertising. STAR*D aims at enrolling self-declared patients from active primary and specialty care practices. The feasibility and the adaptations needed for this approach remain to be defined.

Methods: Clinical Research Coordinators are provided to active clinical practice sites to screen, consent, enroll, and assist in the conduct of research and clinical assessments and to guide the implementation of the treatment protocol. A brief rating, the 16-item Quick Inventory of Depressive Symptoms, is obtained at each clinic visit, as are global ratings of side effect frequency, intensity, and overall burden. These measures help provide uniformly gathered information to the prescribing clinician who must adjust medication dosages based on a clinician manual. Research outcome assessors conduct telephone interviews to obtain primary symptomatic outcomes. Interactive Voice Response (IVR) methods are used to obtain measures of daily function, side effects, and service utilization.

Results: Data on the first 1,000 participants reveals a robust enrollment rate (over 100 subjects per month), a high rate of completion of Research Outcome Assessments (>90%), and an acceptable rate (76%) of completed IVR calls. A data and clinician feedback system to optimize the implementation of the treatment protocols was developed and to date has resulted in high treatment protocol adherence. No completed suicides have occurred.

Conclusions: STAR*D has demonstrated that enrollment, retention, the delivery of high quality protocol-driven treatment by nonresearch clinicians, and the acquisition of research outcomes is feasible and safe in active primary and specialty care practices.

Source of Funding: NIMH Contract N01-MH-90003

Session II – 25

Does Pre-treatment Anxiety or Insomnia Predict Acute Response to Bupropion SR?

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Background: Some clinicians believe that noradrenergic/dopaminergic agents are less effective for depressed patients with substantial levels of pretreatment anxiety or insomnia. This retrospective analysis was conducted to determine whether higher levels of anxiety or insomnia at baseline were associated with poorer antidepressant response of slower onset of response to bupropion sustained release (SR).

Method: A retrospective analysis was conducted using data from an open-label, 8-week, acute phase multicenter study in 796 adult outpatients with recurrent, major depressive disorder who received bupropion SR (300 mg/day). Depressive symptom severity was measured by the 17-item Hamilton Rating Scale for Depression (HAM-D_{17}). Anxiety symptoms were measured by the 14-item Hamilton Rating Scale for Anxiety (HAM-A). Insomnia was assessed by totaling the 3 HAM-D_{17} insomnia items (early, middle, and late insomnia).

Results: Overall, 67% (533/796) of patients responded to treatment (response defined as ≥50% reduction in baseline HAM-D_{17} total score) and 56% (442/796) achieved remission (exit HAM-D_{17} total score ≤7) (intent-to-treat sample). Neither baseline anxiety nor baseline insomnia was related to the likelihood of antidepressant response. Furthermore, there was no relationship between time to onset of either anxiolysis or antidepressant response and severity of baseline anxiety or insomnia. However, baseline anxiety, but not insomnia, was related to the likelihood of remission.

Conclusion: Antidepressant response rates and time to onset of response were similar in outpatients with and without high levels of baseline insomnia or anxiety treated with bupropion SR. Pretreatment severity of anxiety or insomnia are not clinically useful in predicting which depressed outpatients will benefit from bupropion SR.

Source of Funding: GlaxoSmithKline

Session II – 26

Poor Sleep is Associated with Poor Acute Treatment Response in Major Depression

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Background: Insomnia and sleep electroencephalographic (EEG) characteristics have been associated with worse treatment outcomes in patients with major depressive disorder (MDD). However, previous studies have involved individual clinical trials with relatively small numbers of subjects and single treatment modalities. The goal of this secondary analysis was to examine the relationship between pre-treatment sleep complaints, sleep EEG characteristics, and short-term treatment outcomes in a large sample of patients with MDD.

Methods: Subjects included 546 patients with MDD (175M, 371F, age 20-91y) drawn from five clinical trials involving acute and maintenance treatment. Treatments included pharmacologic treatment (imipramine, nortriptyline) and/or interpersonal or cognitive behavioral psychotherapy. Stabilization, the major outcome, was defined as a score of $\leq$7 on the Hamilton Rating Scale for Depression (HRSD) over two consecutive monthly assessments. Multivariate logistic regression models and signal detection models were used to identify significant clinical correlates (derived from items on the HRSD) and significant sleep EEG correlates of stabilization, after adjusting for age, sex, and medication treatment.

Results: 67% of subjects met the stabilization criterion. Non-stabilization was significantly related to increased age and female gender, but not medication treatment. Using multivariate logistic regression models, initial insomnia on the HRSD ($p=0.005$) and overall HRSD severity ($p=0.02$) were significantly associated with non-stabilization; middle and late insomnia, anxiety, and random selections of HRSD items were not. Among sleep EEG measures, sleep latency ($p=0.002$), sleep efficiency (time spent asleep/time in bed) ($p=0.003$), and sleep maintenance (sleep efficiency less sleep latency) ($p=0.02$) were significantly related to non-stabilization. Using a variety of signal detection models, the most consistent correlates of non-stabilization were sleep latency $\geq$28 minutes on sleep EEG, age $\geq$62, and initial insomnia of >30 minutes on the HRSD.

Conclusion: This re-analysis suggests that a simple clinical question ("Does it take you longer than 30 minutes to fall asleep?") identifies a subgroup of MDD patients who are less likely to respond to psychotherapy or pharmacotherapy. EEG sleep results substantiate the same criterion. MDD patients with severe difficulty falling asleep may benefit from other types of acute treatment.

Source of Funding: MH30915, MH 24652, AG00972

Session II – 27

Efficacy of Citalopram as a Monotherapy or as an Adjunctive Treatment to Estradiol for Perimenopausal and Postmenopausal Women with Depression and Vasomotor Symptoms

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Background: In the United States, more than 1,300,000 women are expected to reach menopause every year. The menopausal transition has been associated with the occurrence of various clinical conditions and an increased psychiatric morbidity. Estrogen therapy (ET) is considered the treatment of choice to promote relief of a variety of menopause-related somatic symptoms. In addition, recent placebo-controlled studies demonstrated the efficacy of estradiol for the treatment of depression in perimenopausal women. It is still unclear whether the use of antidepressants alone may alleviate menopause-related mood and vasomotor symptoms, or enhance the response observed with estrogen therapy.

Methods: Peri and postmenopausal women with depressive disorders received treatment with: a) adjunctive citalopram, following an initial 4-week treatment with estradiol (E2) monotherapy, in subjects who failed to respond to E2 (n=13), or b) citalopram alone (n=22). Depressive symptoms, menopause-related symptoms, and global clinical improvement were assessed at baseline and at the end of adjunctive treatment (8 weeks) or citalopram monotherapy (12 weeks). Remission of depression was defined as a score of <10 on the Montgomery-Åsberg Depression Rating Scale (MADRS), and a score of ≤ 2 on the Clinical Global Impression Scale (I-CGI) at study endpoint.

Results: Twelve women (92.3%) concluded the 8-week adjunctive treatment; full remission of depression was observed in eleven subjects (84.6%); there was a significant improvement of residual symptoms that had persisted after an initial 4-week treatment with E2 alone ($p<0.05$). Fourteen subjects concluded the treatment with citalopram monotherapy; thirteen subjects (86.6%) showed full remission of depression. Symptoms of anxiety and other somatic complaints had a significant improvement ($p<0.05$). There was a trend towards improvement in vasomotor symptoms with antidepressant alone ($p=0.06$).

Conclusions: Citalopram is efficacious as an adjunctive treatment for depression in women who remain symptomatic despite the use of estrogen. Citalopram alone is also efficacious for peri and postmenopausal depression. Further investigation should delineate possible synergistic effects of estrogens and antidepressants for menopausal depression, and the role of antidepressants as a treatment for vasomotor symptoms.

Source of Funding: Supported by a National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award (Dr. Soares, 2001 Callaghan Investigator), and by a research grant from Forest Laboratories, USA.

Session II – 28

Serum Folate and Homocysteine as Predictors of Clinical Response to Treatment in Fluoxetine-Resistant Major Depressive Disorder

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Objective: In a previous study we found that the presence of low folate levels conferred poorer response to open treatment with fluoxetine in patients with Major Depressive Disorder (MDD). In the present study we assessed the relationship between serum folate and homocysteine levels and clinical response in MDD patients who had previously failed to respond to open treatment with fluoxetine 20 mg/day and were enrolled in a 4-week, double-blind trial of 1) high-dose fluoxetine, 2) lithium augmentation of fluoxetine or 3) desipramine augmentation of fluoxetine.

Methods: 55 outpatients (mean age: 41.4 years; 21 women) with MDD enrolled in the double-blind trial had serum folate and homocysteine measurements at baseline (prior to fluoxetine treatment initiation). Folate levels were classified as either low (≤2.5 ng/ml) or normal. Homocysteine levels were classified as either elevated (≥13.2μmol/liter) or normal. With the use of separate logistic regressions we then assessed the relationship between homocysteine and folate level status and clinical response to the double-blind phase.

Results: The presence of low folate (p=0.03) or elevated homocysteine levels (p=0.04) was associated with poorer response to treatment. The response rates for patients with and without low folate levels were 7.1% versus 44.7%, respectively. The response rates for patients with and without elevated homocysteine levels were 13.3% versus 45%, respectively.

Conclusion: Low serum folate levels and elevated serum homocysteine levels were found to place patients with fluoxetine-resistant MDD at risk for further treatment resistance.

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Session II – 29

Venlafaxine and SSRIs: Comprehensive Pooled Analysis of Remission in Depression

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Objective: Prior research suggested that venlafaxine, which has been reported to act as a dual serotonin and norepinephrine reuptake inhibitor, may be more effective than selective serotonin reuptake inhibitors (SSRIs) as a class. We now report results of a pooled analysis of original data from 33 randomized, double-blind comparative studies of venlafaxine/venlafaxine extended-release (XR), SSRIs, and placebo.

Methods: Remission (HAM-D_{17} score ≤ 7) rates were evaluated in 7463 depressed patients treated with venlafaxine/venlafaxine XR (n=3300), SSRIs (n=3236; 1673 fluoxetine, 680 paroxetine, 652 sertraline, 197 citalopram, 34 fluvoxamine), or placebo (n=927) for, ≤ 8 weeks. Odds ratios for remission (and 95% confidence intervals) were also calculated for venlafaxine versus the SSRIs.

Results: Overall remission rates were venlafaxine, 41% (1364/3300); SSRIs, 35% (1121/3236); and placebo, 24% (225/927). All comparisons were statistically significant for remission and for 7 of 7 alternate measures of antidepressant efficacy ($P<0.001$). Individual comparisons revealed greater remission rates for venlafaxine versus fluoxetine (42% vs 34%; $P<0.001$), paroxetine (44% vs 39%; $P<0.001$), and the other SSRIs (37% vs 32%; $P<0.001$). The overall odds ratio (OR) for remission was 1.309 (95% CI 1.181-1.451), favoring venlafaxine over SSRIs. Individual ORs were 1.413 (95% CI 1.221-1.635) for venlafaxine versus fluoxetine; 1.203 (95% CI 0.970-1.492) for venlafaxine vs paroxetine; and 1.164 (95% CI 0.925-1.464) for venlafaxine vs sertraline.

Conclusion: These results confirm prior research suggesting the significantly greater likelihood of achieving remission of depression with venlafaxine versus fluoxetine and perhaps other SSRIs.

Source of Funding: Wyeth Research

Session II – 30

Remission Rates Following Therapy with Bupropion or Selective Serotonin Reuptake Inhibitors

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Background: Major depression is a chronic and recurring disorder. Longitudinal studies suggest patients who achieve full remission of depression following acute treatment are less likely to relapse. Therefore, it has been proposed that remission is the best criterion to compare the relative efficacy of various antidepressant therapies.

Objective: To compare the remission rates during treatment with bupropion or the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, or paroxetine.

Methods: Data were pooled from seven randomized, double-blind, controlled, acute-phase studies of major depressive disorder. Patients received bupropion SR 100-400mg/day (n=688), bupropion IR 225-450 mg/day (n=60), fluoxetine 20-60mg/day (n=348), sertraline 50-200mg/day (n=358), paroxetine 10-40 mg/day (n=52) or placebo (n=524). Remission rates (17-item Hamilton Rating Scale for Depression score ≤7) were calculated at 8 weeks in 5 studies and at 6 weeks in the 2 studies of 6-week duration.

Results: Remission rates with bupropion and SSRIs (fluoxetine, sertraline, and paroxetine) were similar and consistent across trials (bupropion 47.1%, SSRIs 47.3%) and remission rate with bupropion was superior to placebo (36.1%, $p<0.01$). The four active treatments were well-tolerated with similar adverse event profiles. The SSRIs were associated with a greater incidence of orgasm dysfunction (37.5%) compared to bupropion (11.7%, $p<0.01$) and placebo (11.3%, $p<0.01$).

Conclusions: Remission rates with bupropion were superior to placebo and no different than remission rates following treatment with an SSRI. All medications were well-tolerated with the exception of a greater incidence of orgasm dysfunction among patients receiving an SSRI.

Source of Funding: GlaxoSmithKline

Session II – 31

Onset of Antidepressant Activity of Olanzapine/Fluoxetine Combination in Patients with Bipolar Depression

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Introduction: Rapid onset of action in an antidepressant would have several advantages, particularly in patients with more severe or difficult-to-treat depressions such as bipolar depression: prevention of suicide, reduced hospitalization, and, most importantly, prompt relief for patients who are suffering. The present study investigated the onset of action and time to sustained response of olanzapine/fluoxetine combination (OFC) using data from a study (n=833) designed to compare OFC with olanzapine and placebo for treating bipolar depression.

Methods: The primary efficacy measure was the Montgomery-Åsberg Depression Rating Scale (MADRS). Analyses included traditional analysis (group mean comparisons at week 1), pattern analysis, mixed-effects curvilinear regression, and survival analysis of sustained response. Area under the curve analysis, which incorporates both onset and global effect, was conducted to assess overall effectiveness.

Results: Traditional analysis revealed significantly greater improvement in MADRS scores at week 1 for OFC versus placebo (-9.55 vs. -5.08, $p<.001$) and for olanzapine versus placebo (-8.31 vs. -5.08, $p<.001$). MADRS change from baseline to week 1 for the OFC group was significant versus placebo at $p<.05$ for 6 of the 10 individual MADRS items. Pattern analysis revealed that OFC had a significantly greater percentage of early persistent responders (defined as response within two weeks and not followed by a relapse) than the olanzapine or placebo groups (32.4% vs. 18.3%, $p<.05$; and 12.7%, $p<.001$, respectively). Survival analysis of sustained response revealed a significantly shorter time to sustained response for OFC versus placebo ($p<.001$) and versus olanzapine ($p<.05$). Mixed-effects curvilinear regression analysis revealed a significant therapy by time interaction ($p<.001$). Area under the curve analysis revealed a significantly greater percentage of total possible improvement (48.2%) for OFC vs. olanzapine (38.5%, $p<.01$) or placebo (27.8%, $p<.001$).

Conclusion: OFC and olanzapine demonstrated significantly faster onset of action compared to placebo as measured by traditional analysis. Patients treated with OFC had significantly shorter time to sustained response, greater likelihood of early persistent response, and greater global effect than either olanzapine or placebo. Overall, OFC demonstrated rapid and sustained antidepressant action in a sample of bipolar depressed patients.

Source of Funding: Research supported by Eli Lilly and Company.

Session II – 32

Assessing Onset of Action in Clinical Trials of Duloxetine 60 mg QD

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Objective: Measuring the time to onset of clinically meaningful antidepressant efficacy presents a challenge in methodology (Montgomery, 2002). In addition to reaching consensus on a definition of "meaningful improvement", issues to be addressed include: (i) Patient-rated depression scales may portray a more delayed onset of action than clinician-rated scales; (ii) Overall rating scale scores may be less sensitive to change than those of derived subscales (Faries, 2000); (iii) Assessments of time to sustained, as opposed to initial, symptom improvement can yield surprisingly different results.

Methods: Efficacy data were pooled from two identical but independent 9-week randomized, double-blind clinical trials of duloxetine 60 mg QD (N=244) and placebo (N=251). Efficacy measures included the $HAMD_{17}$ total score, $HAMD_{17}$ Maier subscale, Clinical Global Impression of Severity (CGI-S), and Patient Global Impression of Improvement (PGI-I).

Results: Improvement in mean global impression scores was significantly greater for duloxetine compared with placebo after 1 week (CGI-S) or 2 weeks (PGI-I) of treatment. Significantly greater improvements for duloxetine-treated patients compared with placebo were observed after 1 week based on mean $HAMD_{17}$ Maier subscale score and after 2 weeks based on mean $HAMD_{17}$ total score. Median time to initial 20% improvement in Maier subscale score was 14 days for duloxetine-treated patients vs. 21 days for placebo ($p<.001$), whereas median time to *sustained* 20% Maier subscale improvement was 21 days for duloxetine vs. >63 days for placebo.

Conclusions: In this study, onset of antidepressant action for duloxetine (60 mg QD) occurred within 1-2 weeks based upon results from a wide range of symptom improvement measures.

Source of Funding: Eli Lilly and Company

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Session II – 33

The Impact of Cardiovascular Risk Factors on Treatment Outcome in MDD

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Objective: We examined the impact of cardiovascular risk factors on treatment outcome among patients with MDD in the acute and in the continuation treatment phases.

Method: 348 subjects meeting DSM-III-R criteria for MDD, ages 19 to 65, (192 females, 55.2%) enrolled in an 8-week treatment study with fluoxetine 20 mg/day. We recorded for each subject the age, gender, smoking status, family history, cholesterol, arterial hypertension, diabetes, concomitant medications. We calculated a cumulated cardiovascular risk score (range = 0-6) following the NIH ATP III guidelines (based on the Framingham Heart Study). The 17-item Hamilton Rating Scale for Depression (Ham-D) was administered five times during the treatment to assess changes in depressive symptoms. The outcome variables were: treatment response (Ham-D reduction $\geq$ 50%) and remission (final Ham-D $\leq$ 7). Among subjects who had achieved remission, 119 patients (63 females, 53%) were followed for 28 weeks of continued treatment with fluoxetine 40 mg/day. We used logistic regression to assess the relationship between cardiovascular risk factors and clinical outcome.

Results: Subjects with cardiovascular risk scores $\geq$ 4 (n=38) had significantly lower rates of treatment response (44.7%, p=.023), and remission (39.5%, p=.038), compared to subjects with cardiovascular risk scores of 2 or 3 (n=116; response: 53.4%; remission: 47.4%), or those with cardiovascular risk scores of 0 or 1 (n=194; response: 62.4%; remission: 55.7%). The total cardiovascular risk score was significantly related to treatment non-response (p=.021) and lack of remission (p=.044). Among individual cardiovascular risk factors, elevated total cholesterol was a significant predictor of non-response (p<.01), and lack of remission (p=.011). The total cholesterol level also significantly predicted the relapse of MDD during the continuation phase. (p<.05).

Conclusion: In MDD patients, the total burden of cardiovascular risk factors significantly predicts lack of response and remission after antidepressant treatment with fluoxetine. Elevated total cholesterol level was associated with lack of response and remission in the acute treatment phase, as well as with increased rates of MDD relapse in the continuation phase of antidepressant treatment.

Source of Funding: Supported in part by NIMH grant R01-MH48483 (Dr. Fava)

Session II – 34

Changes in QEEG Cordance Predict Response in Treatment Resistant Depression and in Reboxetine Monotherapy

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Objective: Cordance is an EEG measure correlated with regional cerebral perfusion and metabolism [1,2]. In studies in unipolar major depression (MDD) [3,4], decreases in prefrontal cordance early in treatment were associated with response in subjects who were medication-free prior to the initial EEG and treated with either fluoxetine or venlafaxine, medications with effects on serotonin or serotonin and norepinephrine respectively. We investigated the generalizability of this work by hypothesizing: [A] cordance decreases would be associated with response in treatment resistant depression (TRD) subjects without wash-out between treatments, and [B] cordance changes would be associated with response to reboxetine [REB], a more purely noradrenergic antidepressant.

Methods: In both study groups, multi-channel, awake, resting EEGs were recorded from adults with MDD as previously described [3,4]. Prefrontal cordance was determined by averaging values at Fp1, Fp2 and Fpz electrodes. Responders were *a priori* defined as exhibiting HAM-D $\leq$ 10 at the end of treatment. [A] TRD subjects (n=11) had failed open-label SSRI monotherapy and were starting a new treatment at enrollment in this study; EEG data were recorded prior to the new regimen and after 1 week of treatment. Treatment decisions were made naturalistically by their treating psychiatrists. [B] REB subjects (n=25) were enrolled in an 8-week treatment trial with reboxetine (8 - 10 mg/d). EEG recordings were made at pretreatment baseline and after 48 hrs, 1, 2, 4, and 8 weeks of treatment.

Results: [A] 6 of 11 TRD subjects responded to treatment. Cordance decreases were seen in 5/6 responders, and only 2/5 non-responders, yielding test sensitivity 83% and specificity 60%. [B] 14 of 25 REB subjects responded. Cordance decreased in the responder subjects, with mean changes in cordance between groups showing differences at week 1 ($p=0.038$); clinical differences emerged at week 4.

Conclusions: In both TRD and REB subject groups, early cordance decreases characterized responders to treatment. These findings are consistent with prior reports with SSRI or mixed SSRI/SNRI monotherapy, with washout prior to treatment. These prospective evaluations support the study of cordance biomarkers in treatment response, and suggest that it may be used both [A] in effectiveness trials in TRD that parallel clinical practices without wash-out between treatments and [B] with antidepressants with diverse mechanisms of action.

Source of Funding: Aspect Medical Systems, Inc., NIMH. Reboxetine compound was supplied by Pharmacia/Upjohn.

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Session II – 35

Analysis of Gepirone-ER on the Bech-6 and Individual HamD-17 Item Scores

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Objective: To evaluate the effect of the $5HT_{1A}$ agonist gepirone-ER on core depressive symptoms of depression as measured by the Bech-6 and individual HamD-17 items.

Methods: This 8-week, double-blind, placebo-controlled study of gepirone-ER was conducted in patients aged 18-70 who met DSM-IV criteria for Major Depressive Disorder. Patients were randomized to placebo or gepirone-ER, which was initiated at 20 mg/d for 3 days, increased to 40mg/d with titration to 80mg/d per investigators' discretion. Participants were evaluated at baseline and weeks 1, 2, 3, 4, 6, and endpoint, week 8.

Results: In 204 patients, gepirone-ER produced a statistically significant difference compared to placebo for the mean change in HamD-17 total score at weeks 3 and 8. Further analysis revealed that gepirone-ER caused a statistically significant decrease from baseline on the Bech-6 at all study visits compared to placebo. Statistically significant improvements were also found between baseline and endpoint visits in the following HamD-17 items: depressed mood, work and activity, genital symptoms, psychic anxiety, and psychic retardation. The most commonly reported adverse events were dizziness, headache, and nausea.

Conclusion: The Bech-6 and individual HamD-17 item scores showed statistically significant improvement compared to placebo, which, when taken together, lend support to gepirone-ER's efficacy in the treatment of major depressive disorder. Further, the Bech-6 was shown to be more sensitive to the effect of gepirone-ER than was the HamD-17.

Source of Funding: Organon, Inc.

Session II – 36

Sertraline Treatment for Depression Post ACS Reduces Total Treatment Costs

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Background: Patients with major depression after hospitalization for acute coronary syndromes (ACS) are at a 3 – 4 fold increased risk of cardiovascular death. SADHART demonstrated the safety and efficacy of sertraline in patients with major depression following hospitalization for myocardial infarction or unstable angina. The purpose of this analysis was to compare the costs of major cardiovascular events, revascularization procedures, and psychiatric hospitalizations in the patients treated with sertraline versus placebo in the SADHART trial.

Methods: Hospitalization rates for cardiovascular events, revascularization procedures, and psychiatric hospitalizations were determined from serious adverse event reports and Duke University Clinical Research Institute Clinical Events Committee records from the SADHART trial. Healthcare costs associated with these events were derived from the 2002 Medicare DRG schedule for inpatient hospitalizations.

Results: There were significantly fewer hospitalizations and revascularization procedures in the sertraline treated group compared with placebo (55 vs. 74; p=0.037), resulting in a lower average treatment cost per patient. After including the cost of 6-months of treatment with sertraline, there was a net cost savings of over $350 per patient in the treated vs. placebo group.

Conclusion: Treatment of depression with sertraline in patients recently hospitalized for ACS resulted in a significant reduction in cardiovascular and psychiatric hospitalizations and a net cost savings. These results suggest that a greater effort to identify and treat depression in patients experiencing acute coronary syndromes will not only improve care and quality of life for these patients, but also may lead to cost savings.

Source of Funding: Pfizer, Inc.

Session II – 37

A Preliminary Study of the Effect of Smoking Status on Response Rate in Clinical Trials of Antidepressants

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Background: Individuals diagnosed with depression have more than double the incidence of smoking than non-depressed individuals. Acute administration of nicotine can produce antidepressant activity through the release of biogenic amines. However, this release mechanism, if maintained at a high rate for a prolonged period of time, may deplete the nerve endings of neurotransmitter stores. This could limit the effectiveness of antidepressants which work through inhibiting the inactivation of biogenic amines. Support for this notion was sought by examining response rates of smokers and non-smokers in clinical trials of antidepressants.

Methods: Data from nine consecutive antidepressant clinical trials were examined. Of a total of 246 depressed subjects randomized, 227 had at least one post-randomization assessment and gave a clear indication of current smoking (n=76) or non-smoking (n=151) status. A subset was selected to represent subjects in whom response to drug (and thus limitations in the response to drug) might be expected. This subset (n = 183) was defined by the following criteria: (1) depression of at least moderate severity (HAM-D >= 18) at randomization; (2) the possibility of having been randomized to a medication approved for treatment of depression, at a usually effective dose; and (3) treatment of at least 2 weeks duration. Response rates of smokers and non-smokers were compared, using a 50% reduction in HAM-D_{17} to define response.

Results: Over the nine studies the response rate averaged 44%, with smokers responding less than non-smokers (37% vs 47%). The subset of 183 subjects showed a widened difference, to 42% in smokers and 58% in non-smokers ($p = .03$, Fisher's exact, one-tailed). The ongoing process of unblinding and subsequent exclusion of placebo-treated subjects from the analysis is predicted to widen the difference yet further.

Conclusion: In preliminary data, smokers had lower overall response rates than did non-smokers in antidepressant clinical trials. Effects were more prominent in the subset of subjects expected to benefit the most from antidepressant treatment.

Significance: Differences between smokers and non-smoker in drug response rate merit attention in clinical trials.

Source of Funding: Psychiatric Research Institute

Session II – 38

Daily Assessment of Depression Severity with an Interactive Voice Response System (IVRS)

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Introduction: Depression severity ratings typically reflect symptoms experienced over intervals of about a week, as recalled and reported by patients during interactions with clinicians. Infrequent assessment, imperfect recall, and measurement error limit the precision with which the time of onset of improvement can be determined. We seek to develop an effective means of daily depression severity assessment using an IVRS.

Methods: Patients participating at 26 of the investigative sites in an ongoing clinical trial comparing antidepressants in treatment-resistant depression (TRD) who consented to our voluntary study were asked to make once daily (afternoon or evening) telephone calls to an IVRS for 21 consecutive days. Patients entered ID/password numbers and responded to recorded voice prompts by pushing telephone keypad buttons. Patients rated their sadness, nervousness, irritability, lack of energy (LOE), and difficulty thinking (DT), each on a scale of 0-9. Call dates/times and durations were determined. Patients were not paid for making calls. Sites were not told if/when patients failed to make calls. The IVRS did not make outbound calls to patients. Clinicians rated depression severity after approximately 7 days of calling with the Quick Inventory of Depressive Symptomatology (Rush, in press).

Results: 54 patients made 517 calls. Only 25 patients made >10 calls, but many who made fewer also dropped out early from the TRD trial. In patients who made 2 or more calls, mean inter-call interval was 1.5 (range 1-4) days. Mean call duration was 2.0 (range 1.1-3.9) minutes. Correlation coefficients with sadness were: nervousness r=0.53, irritability r=0.56, LOE r=0.57, and DT r=0.57. Nervousness was correlated with irritability (r=0.68). LOE was correlated with DT (r=0.61). Multiple correlations with QIDS items had correlation coefficients >0.4. Ratings from IVRS calls proximal in time to QIDS assessment correlated better with QIDS items than those more remote.

Conclusions: Daily telephone assessment seems practical and may be a valid means of assessing depression severity and determining time of onset of improvement. Even when calls are brief and easy to make, some patients may comply poorly with daily calling. In future work, calling incentives, compliance feedback, and/or outbound calling may be warranted.

Source of Funding: Eli Lilly and Company

Session II – 39

Memory Enhanced Retrospective Evaluation of Treatment: MERET

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Introduction: Retrospective measures of change require accurate recollection of baseline experiences, however memories of past events often fade with time. Augmentation of patients' memories by use of voice recording and subsequent playback may improve retrospective ratings of treatment-related change.

Methods: Patients participating in a double-blind, placebo-controlled study of acute treatment of major depression with painful symptoms (FIJ-MC-HMCB) could volunteer to pilot test MERET procedures. At baseline, 51 subjects used a telephone to record open-ended responses to prompts asking them to describe how: (1) "you've been feeling emotionally;" (2) "you've been feeling physically;" and (3) "your emotional and physical feelings have affected your general ability to function" during the prior week. At early discontinuation (N=5; mean of 27 days), 7 weeks (N=27; mean of 52 days), and 9 weeks (N = 16; mean of 65 days) later the recordings were played back to subjects. MERET ratings of change since baseline from 'Very Much Better' [1] to 'Very Much Worse' [7] were obtained for emotional, physical, and functional domains, as well as for overall experience. Subjects then rated [0 to 10] how helpful hearing the baseline recordings was.

Results: Mean recording lengths (±SD) to the prompts above were 58 (±48), 36 (±27), and 41 (±35) seconds, respectively. MERET helpfulness ratings were correlated with recording durations (Spearman's rho = .42, p<.001). Change ratings among the domains, and with overall change, were highly correlated (rhos .69 to .86, all p-values<.001). MERET helpfulness ratings ranged from 0 to 10, but were not distributed independently across the overall change ratings (Chi-Square = 23.0, p<.001):

	Very Much Improved	Much Improved	Little Improved	No Change	Little Worse	Much Worse	Very Much Worse
Helpfulness Ratings 0-5	4	5	2	8	2	--	--
Helpfulness Ratings 6-10	--	12	13	1	0	1	--

Conclusion: Results demonstrate technical feasibility of MERET procedures. MERET may be most helpful when patients need to discriminate modest improvement from greater or lesser improvement. Relationships between treatment assignment, MERET ratings, and clinical measures obtained at baseline and endpoint in this study will also be presented.

Source of Funding: Eli Lilly and Company

Session II – 40

Intermittent Use of Venlafaxine (Flexible Dose) in the Treatment of Premenstrual Dysphoric Disorder (PMDD)

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Background: Premenstrual Dysphoric Disorder (PMDD) affects 3% to 8% of women in their reproductive years. Evidence indicates that PMDD may be associated with dysregulation in serotonergic and noradrenergic neurotransmission. Given the apparent rapid onset of improvement in PMDD symptoms following treatment with SSRI's, the appeal of luteal phase treatment for this disorder is intuitive. The current study examines the efficacy of intermittent dosing of venlafaxine (75 to 112.5 mg/day) for the treatment of PMDD, and the risk for treatment emergent discontinuation symptoms associated with such treatment.

Methods: This is an open study, including one cycle as a diagnostic confirmation phase, one cycle as a single-blind placebo phase, and two cycles as a treatment phase. Women aged 18-45 years, with regular cycles and use of an approved birth control method, who did not report recent use of psychotropic agents, and did not meet criteria for any major Axis I psychiatric disorder other than PMDD were recruited for the diagnostic phase. Daily Rating of Severity of Problems (DRSP) forms were used to confirm the diagnosis of PMDD, and throughout the participation in the study. The Discontinuation-Emergent Signs and Symptoms Self-Rated (DESS-SR) checklist was administered to examine the occurrence of symptoms associated with intermittent dosing. Treatment efficacy was measured based on changes in luteal DRSP total scores and sub-scores (depression, physical symptoms, anger, overall functioning). Remission was defined as CGI-severity ≤ 2 at the end of treatment.

Results: One hundred and four subjects entered the diagnostic confirmation phase. Of those, 43 completed at least one cycle of prospective evaluation with DRSP forms. Twenty-four subjects had their diagnosis of PMDD confirmed prospectively, and therefore entered the placebo phase. Six out of 17 subjects who completed the placebo phase were considered placebo responders. Eleven subjects entered the treatment phase. All study completers (N=9) had a significant decrease in luteal DRSP total scores and sub-scores, and overall improvement in functioning ($p<0.05$ for all comparisons, Wilcoxon signed ranks tests). Six of nine women (67%) had CGI scores ≤ 2 at the end of study treatment. No significant discontinuation symptoms were observed.

Conclusions: Intermittent use of venlafaxine is an efficacious and well-tolerated treatment for women who suffer from PMDD.

Source of Funding: Supported by a research grant from Wyeth Laboratories, USA.

Session II – 41

The Sexual Interest and Desire Inventory (SIDI): Development and Pilot Validation

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Introduction: Hypoactive sexual desire disorder (HSDD) is the most common sexual complaint in women. Currently, there are no well-validated instruments useful for assessing the relevant variables related to sexual desire or to track changes in sexual desire as a result of either pharmacological or non-pharmacological treatment. The Sexual Interest and Desire Inventory (SIDI) was developed to meet this need.

Methods: A panel of experts in female sexual dysfunction from academic centers and the pharmaceutical industry was assembled to create a short, empirically validated and easy-to-use inventory. Seventeen items were included in the pilot inventory, including two questions related to mood and fatigue/energy. An innovative grid system of intensity vs. frequency/duration was used to provide a more sensitive and complete assessment of the relevant dimensions of sexual desire such as affection, thoughts, fantasies, receptivity, etc. The SIDI was first tested by administering it to both women with HSDD and a sample of non-HSDD women. The women with HSDD also completed the Changes in Sexual Functioning Questionnaire (CSFQ) to assess convergent validity. Additionally, correlations between SIDI scores and scores on the CSFQ and Female Sexual Function Index (FSFI) were calculated using scores from multiple timepoints in an ongoing clinical trial in female HSDD.

Results: There was no overlap in the distribution of scores for HSDD- and non-HSDD women. There was a high correlation between the scores on the SIDI and the CSFQ for both the pilot validation ($r=0.92$) and the clinical trial ($r=0.68$) studies. Additionally, there was a high correlation between SIDI scores and scores on the FSFI ($r=0.76$).

Conclusions: These preliminary findings show that the piloted version of the SIDI can discriminate HSDD and non-HSDD patients and that SIDI scores correlate well with scores on other measures of female sexual dysfunction. Overall, these results support the validity of the SIDI in assessing female sexual desire.

Session II – 42

Multicenter Study of Bupropion in Female Hypoactive Sexual Desire Disorder

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Objective: Single blind research suggests the efficacy of bupropion for the treatment of idiopathic global hypoactive sexual desire disorder (HSDD) in premenopausal women. This study assessed this hypothesis using a more rigorous research design.

Methods: 72 women (ages 23.7 to 46.2 years) who met operational criteria for hypoactive sexual desire disorder (HSDD) were studied for 4-months in a randomized, placebo-controlled, double-blind, titrated dose multi-site study. Entry criteria included duration of HSDD between 6 months and 10 years, Hamilton Depression and Hamilton Anxiety scores both below ten, stable sexual partner, absence of interpersonal conflict, serum free testosterone equal to or above 1.1 pg/ml at days 20-24 of the menstrual cycle, and absence of other active psychiatric disorder. Response was measured at screening, baseline, day 28, 56, 84, and 112 by the Changes in Sexual Functioning Questionnaire (CSFQ), a 14-item self-report standardized test.

Results: Women receiving buproprion had significantly higher total CSFQ scores at day 28 (45.1±1.1 SEM vs. 41.1±1.3 SEM, t=2.3, p=0.03); scores continued to increase at each time point for women receiving the drug.

C**onclusions:** Bupropion may be effective in a subgroup of premenopausal women with HSDD.

Source of Funding: GlaxoSmithKline

Session II – 43

Efficacy of Sildenafil Citrate in Men with Serotonergic Antidepressant-Associated Erectile Dysfunction: Results of a Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: To evaluate the efficacy of sildenafil citrate (Viagra®) in men with antidepressant (AD)-associated erectile dysfunction (ED).

Methods: Men (≥18 years) with major depressive disorder (MDD) in remission (HAM-D ≤10) who were taking a serotonergic AD for ≥8 weeks (stable dose ≥4 weeks) and experiencing AD-associated ED were randomized to sildenafil or placebo for 6 weeks of double-blind (DB) treatment followed by 6 weeks of open-label (OL) sildenafil. Efficacy was evaluated using the Sexual Function Inventory (SFI; scoring range, 1–6), which assesses erectile function (EF; primary outcome) as well as sexual desire, arousal, orgasm, and overall satisfaction (secondary outcomes). Two other questions assessed the amount of stimulation required to reach orgasm and the time to orgasm (scoring range, 1–5). For all items, a higher score indicated better sexual function.

Results: At DB endpoint (Week 6), sildenafil patients (n=69) had a significantly improved (ie, higher) mean EF score (2.8±0.2) compared with placebo patients (1.9±0.2, $P<0.0001$ [n=69]). With the exception of the item for time to orgasm, sildenafil treatment was associated with significant changes in the other sexual domains relative to placebo (P values <0.03). After OL sildenafil (Week 12), previous DB placebo patients improved their EF scores by 81%, which was the largest improvement followed by a 77% improvement in overall satisfaction. By Week 12, DB sildenafil patients improved their EF scores by 27%. These patients also showed a 31% increase in overall satisfaction.

Conclusions: Sildenafil was effective in treating ED associated with AD therapy for MDD in remission after up to 12 weeks of treatment as measured by the SFI. Sildenafil was also associated with improvements in other aspects of sexual function, including arousal, orgasm, and overall satisfaction.

Source of Funding: Pfizer, Inc.

Session II - 44

Development of Milnacipran, a Dual Reuptake Inhibitor for Treatment of Chronic Pain Associated with Fibromyalgia

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Milnacipran (MIL) is a pharmaceutical currently licensed in parts of Europe, Asia and elsewhere for the treatment of depression, but which has not been available in the United States. Pharmacologically, MIL is a chemically novel, dual acting reuptake inhibitor, distinguished from other dual-acting agents by its preference for noradrenergic (NE) reuptake inhibition over that of serotonin (5-HT). This profile most closely mimics that seen with certain tricyclic antidepressants (TCAs)—particularly amitriptyline--while lacking the other receptor interactions that underlie TCA side effects and which can limit their tolerability. MIL in clinical use has proven to have a superior safety profile to TCAs. Based on this pharmacological and clinical profile, we postulated that potential therapeutic uses for MIL might include treatment of chronic pain states, including the so-called Functional Somatic Syndromes (FSS) such as Fibromyalgia Syndrome (FMS) and Irritable Bowel Syndrome (IBS). Fibromyalgia, as well as many of the other FSS, fall between the traditional separation between medical and psychiatric illness, and share a similar spectrum of symptoms, predominantly pain, sleep disturbance, fatigue, and depressed mood. These syndromes are common, in some estimates accounting for up to 60% of primary care visits in the U.S. **Methods:** A 12 week randomized, double-blind, placebo-controlled, multi-center Phase 2 trial was conducted to evaluate MIL in patients with a diagnosis of FMS. Patients were escalated weekly from 25 mg to 50, 100 and finally 200 mg daily, or until dose limiting toxicity became evident. Patients randomized to MIL were also randomized to either a once- (QD) or twice per-day (BID) dosing in a blinded fashion. During the study, participants were asked to carry an electronic diary and record pain, fatigue, sleep and quality of life information. This custom diary captured spontaneous clinical pain data in several ways, including: 1) random daily prompts (the device notified the patient to record their current level of pain 4-5 times per day), 2) a daily morning prompt querying about the previous 24-hours' pain and 3) a weekly report asking about average pain for the past week. The electronic assessments were supplemented with traditional pain and QOL inventories during monthly clinic visits. The primary outcome measure was based on change in average pain recorded on the electronic diary, calculated as a weekly average, comparing baseline (two weeks prior to randomization) to endpoint (last two scheduled weeks on treatment). Secondary outcome measures included patient global impression of change (PGIC), Beck scores, the fibromyalgia impact questionnaire (FIQ), the McGill (SF-MPQ) and SF-36 inventories, and sleep and fatigue assessments. Patient pain data collected from the diaries was analyzed by group, comparing the two MIL groups to placebo. All data was analyzed using intent-to-treat methodology (ITT), and missing values were handled using last-observation-carried-forward approaches (LOCF). Two methods for the determination of treatment efficacy were employed. In the first analysis, mean changes in pain scores from baseline to endpoint were compared across treatment groups. The null hypothesis was that there was no difference in pain reduction between placebo and either of the milnacipran treatment groups. In the second analysis, the number of patients in each treatment group who experienced a clinically meaningful response was compared (binary analysis). The null hypothesis was that the rate of response did not differ by treatment group. For purposes of this trial, a 50% reduction in pain intensity was adopted as the definition of a clinically meaningful response. As the pain scores on the diary were based on the Gracely pain scale, a 4.0 Gracely unit reduction was used as the 50% intensity reduction equivalent. **Results:** During the course of this clinical trial, 184 patients were screened for inclusion, and 125 were randomized to receive either milnacipran or placebo treatment. Patients treated with MIL BID experienced statistical improvement in pain scores as compared to the placebo group on both the binary and continuous pain analyses. MIL QD treated patients did not exhibit the same degree of pain reduction, indicating that dosing frequency is important with this formulation of MIL for pain treatment. On a binary basis, the response rate in the BID group was 37% on an ITT basis, 22% for the QD group, and 14% for placebo. BID vs. placebo was statistically significant at $p=0.04$. In contrast, both MIL groups were statistically improved over placebo on the PGIC endpoint ($p=0.003$) as well as multiple components of the FIQ and SF-MPQ inventories.
Conclusion: In this Phase II randomized and controlled clinical trial, twice daily dosing of milnacipran (100 mg BID) was associated with statistically significant improvements in multiple measures of clinical pain in patients with a diagnosis of FMS. Other symptom domains, including fatigue, mood, and patient global improvement reports were nearly equally improved in both milnacipran dosing groups, reaching statistical significance on many of these secondary measures. This dissociation may suggest that alternative pathophysiological mechanisms are operative within different symptom domains of FMS. A Phase III development program, to start later this year, is currently being planned to confirm and extend these findings.

Session II – 45

Comparison of Venlafaxine XR and Paroxetine in the Short-Term Treatment of SAD

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Introduction: Two studies investigated the efficacy, safety, and tolerability of venlafaxine extended release (XR) in the treatment of generalized social anxiety disorder (SAD) in comparison with those of placebo and paroxetine.

Methods: Study 1 (n = 434) and study 2 (n = 429) were randomized, double-blind, multicenter studies. Patients were randomly assigned to receive a flexible dose of venlafaxine XR (75 to 225 mg/day), a flexible dose of paroxetine (20 to 50 mg/day), or placebo for up to 12 weeks. The primary efficacy variable was the Liebowitz Social Anxiety Scale total score. Secondary efficacy variables included the Clinical Global Impression-Severity score, Social Phobia Inventory (SPIN), and responder status (based on Clinical Global Impression-Improvement score ≤ 2).

Results: The scores with both active treatments were significantly better than those with placebo on each efficacy measure listed, using last-observation-carried-forward analysis. The only significant difference between active treatments was observed in study 2, in which the SPIN scores with venlafaxine XR were significantly superior to those for paroxetine at weeks 1 and 2. Treatment-emergent adverse events were similar in the 2 studies and included nausea, insomnia, somnolence, asthenia, dry mouth, and dizziness.

Conclusion: Venlafaxine XR and paroxetine are effective short-term treatments for generalized SAD, with a potential advantage for venlafaxine XR over paroxetine in terms of earlier symptomatic relief.

Source of Funding: Wyeth Research

Session II – 46

Efficacy of Sertraline in Acute Treatment of Generalized Anxiety Disorder (GAD): Item and Factor Analyses

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Background: Several different classes of medications have demonstrated efficacy in the treatment of GAD (with each class having relatively greater efficacy in one or other of the two HAM-A factors, somatic or psychic). These treatments include benzodiazepines (somatic > psychic), TCAs and SSRIs (psychic > somatic), azapirones (psychic > somatic), and most recently pregabalin (an alpha-2-delta agent; psychic = somatic). The goal of this investigation was to evaluate the differential efficacy of sertraline in treating specific HAM-A factors and items in patients with GAD.

Methods: Adult outpatients were eligible for entry who met DSM-IV criteria for GAD with a minimum HAM-A total score $\geq$ 18 (anxiety and tension items each $\geq$ 2). After completion of a single-blind placebo lead-in period patients were randomized to 12 weeks of double-blind treatment with placebo (N=188; female, 51%; mean age, 42 years; baseline HAM-A, 25) or flexible doses (50-150 mg) of sertraline (N=182; female, 59%; mean age, 40 years; baseline HAM-A, 25). The primary outcome measure was the Hamilton Anxiety Rating Scale (HAM-A). Secondary outcomes included the 7-item HAM-A psychic anxiety factor (items #1-6, 14) and the HAM-A somatic anxiety factor (items #7-13).

Results: Treatment with sertraline resulted in significantly greater LOCF-endpoint improvement than placebo on both the HAM-A psychic factor (-6.7 ± 0.4 vs. -4.1 ± 0.4; $p < 0.0001$) and the HAM-A somatic factor (-5.0 ± 0.3 vs. -3.9 ± 0.3; $p < 0.02$). Significant separation from placebo was seen from week 4 on the psychic factor, and at weeks 4 and 12 for the somatic factor. At week 4, the sertraline group demonstrated a similar reduction in both the HAM-A psychic (32%) and somatic factors (32%). By week 12 (LOCF) there was a greater reduction in the psychic (50%) vs. the somatic factor (45%) in the sertraline group, with effect sizes of 0.541and 0.26 respectively. All 7 items of the HAM-A psychic factor were significantly more improved on sertraline vs. placebo, in comparison to 3 of 7 items of the somatic factor.

Conclusion: Sertraline treatment resulted in significant improvement in both the psychic and somatic symptom clusters.

Source of Funding: Pfizer, Inc.

Session II – 47

Placebo-Controlled Trial of Fluoxetine Vs. Fluoxetine Plus Olanzapine in OCD

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Background: One of the few medication combination approaches to obsessive-compulsive disorder (OCD) with encouraging support is the addition of an antipsychotic to a serotonin reuptake inhibitor (SRI). The specific aim of this trial was to determine whether combined treatment with fluoxetine and olanzapine was effective in treating OCD subjects who were "partial" or "nonresponders" to a prospective 8-week trial of open-label fluoxetine.

Methods: Seventy-four subjects with OCD were treated with up to 40 mg fluoxetine. The study consisted of the forty-four subjects who were either "nonresponders" to fluoxetine (<25% reduction in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) from baseline) or "partial" responders with a ≥25% reduction by Y-BOCS but remained symptomatic (OC symptoms of at least moderate CGI severity; and Y-BOCS score of ≥16). These subjects were enrolled in a 6-week placebo-controlled addition of olanzapine (5 mg up to 10 mg). The primary analysis utilized longitudinal data analysis of Y-BOCS scores by repeated measurements ANOVA.

Results: Both fluoxetine plus olanzapine (decrease of 5.1 (SD=4.9), n=22) and fluoxetine (decrease of 3.8 (SD=3.8), n=22) groups improved significantly by Y-BOCS scores over 6 weeks (p=<.0001). However, the treatment by time interaction for Y-BOCS scores was not significant (p=0.16) for olanzapine (6.1 mg mean dose) versus placebo addition to fluoxetine and was not significant (p=0.23) for CGI-Severity. In a subgroup analysis of "nonresponders" (n=21) to fluoxetine, a trend for Y-BOCS scores (p=0.09) was observed for olanzapine (decrease of 5.7 (SD=6.3), n=9) versus placebo addition to fluoxetine (decrease of 2.8 (SD=4.0), n=12).

Conclusion: These findings indicate no additional advantage of adding olanzapine for 6 weeks in OCD patients who have not had a satisfactory response to fluoxetine up to 40 mg for 8 weeks compared to continuing fluoxetine for 6 more weeks.

Source of Funding: MH45802 and medication by Eli Lilly & Company

Session II – 48

The Selective GABA Reuptake Inhibitor Tiagabine for the Treatment of Generalized Anxiety Disorder

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Objective: Gamma-aminobutyric acid (GABA) is the main CNS inhibitory neurotransmitter and plays a key role in the pathophysiology of anxiety and sleep. Tiagabine (Gabitril™), a selective GABA reuptake inhibitor (SGRI), enhances normal GABA tone and has been shown to reduce anxiety and improve sleep quality in preliminary reports. This open-label study evaluated the efficacy and safety of tiagabine in patients with generalized anxiety disorder (GAD).

Methods: This 10-week, randomized, open-label, positive-controlled, blinded-rater study enrolled patients with a primary disorder of GAD. Patients received 4 mg of tiagabine (dosed bid, in the morning and evening) or 20 mg of paroxetine (evening) during the first week of treatment. These doses were increased for optimum response by 2 mg every 3 days for tiagabine (≤ 16 mg/day) or 10-20 mg every 7 days for paroxetine (≤ 60 mg/day). Efficacy was assessed using the Hamilton Rating Scale for Anxiety (HAM-A) and Pittsburgh Sleep Quality Index (PSQI).

Results: A total of 40 patients were randomized to either tiagabine (n=20) or paroxetine (n=20). The mean doses were approximately 9 mg/day tiagabine (bid) and 27 mg/day paroxetine (evening). Tiagabine and paroxetine reduced anxiety, as shown by a significant decrease in mean HAM-A total scores at endpoint (both $P<0.0001$ vs baseline). Furthermore, both treatments significantly decreased mean scores of the HAM-A psychic and somatic anxiety subscales by endpoint (all $P<0.0001$ vs baseline). Tiagabine and paroxetine also improved sleep quality, as indicated by a significant reduction in mean PSQI scores by endpoint ($P<0.0001$ and $P<0.01$, respectively, vs baseline). The most commonly reported adverse events (AEs) for tiagabine were headache (n=11), nausea (n=7), and loss of appetite and dizziness (both n=6) and for paroxetine were headache (n=8), dry mouth (n=5), and nausea and insomnia (both n=4). Sexual dysfunction was reported only by patients in the paroxetine treatment group (n=3). Withdrawal rates due to AEs were low: 5% for tiagabine and 10% for paroxetine.

Conclusion: Tiagabine and paroxetine improved GAD and sleep quality. Tiagabine may represent a therapeutic option for patients with anxiety. These findings support the need for further evaluation of the SGRI tiagabine in the treatment of anxiety.

Source of Funding: Supported by funding from Cephalon, Inc.

Session II – 49

An 8-Week, Double-Blind, Randomized Comparison of Sertraline and Paroxetine for the Treatment of Generalized Anxiety Disorder

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Background: Few studies have compared the efficacy and tolerability of different SSRI medications for the treatment of generalized anxiety disorder (GAD). Recently, paroxetine received FDA approval as a treatment for GAD. Theoretically other SSRIs should also have equivalent efficacy for this condition, given their common therapeutic mechanism of action. We tested the equivalence of the SSRI sertraline to paroxetine in a double-blind, controlled trial.

Methods: Thus far, 25, medication-free, DSM-IV GAD patients (21 F; 4 M; mean±SD age=41±15yrs; baseline HAM-A mean score±SD= 23±7; baseline mean score±SD CGI-severity = 4.2±0.5) were randomized to sertraline (target dose=100 mg/d) or paroxetine (target dose=40 mg/d) treatment for an 8-week period utilizing a flexible-dosing strategy. Primary assessment measures were the Hamilton Anxiety Scale (HAM-A), the Indiana University Generalized Anxiety Measurement Scale (IU-GAMS), and Clinician Global Impression of Illness Severity (CGI-S). Adverse events were monitored using the SAFTEE questionnaire. We conducted a blinded, preliminary analysis on our data.

Results: At this point, patients have responded equivalently to drug A and drug B based on a responder definition of 50% drop in HAM-A ratings over the treatment period (completer responder analysis; Drug A group =5/9 responders vs Drug B group =5/9; Fisher's Exact test 2-tailed p=1.000). Similar findings were evident for the IU-GAMS and CGI-S data. Both treatment groups have reported only mild adverse events.

Discussion: The data, thus far, suggest that sertraline may be comparable to paroxetine in its clinical efficacy and tolerability for GAD.

Source of Funding: Supported by an unrestricted educational grant from Pfizer

Session II – 50

A Comparison of the Response to Sertraline in Children and Adolescents with Major Depressive Disorder

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Background: Major depressive disorder (MDD) is a serious and often relapsing medical problem in children and adolescents. Selective serotonin reuptake inhibitors (SSRIs) are regarded to be the drug treatment of choice for MDD in this population, though it is unclear whether treatment is tolerated equally in both age groups. The current studies assessed the safety, tolerability and efficacy of sertraline in children (6-11 years) and adolescents (12-17 years) with MDD.

Methods: 177 children and 199 adolescents were randomized to receive flexibly-dosed sertraline (50-200 mg/day) or matching placebo for up to 10 weeks. 141 children and 158 adolescents completed 10 weeks of blinded therapy and, of these, 109 children and 117 adolescents were enrolled in a 24 week open-label extension study. The primary efficacy measure was the Children's Depression Rating Scale – Revised (CDRS-R) total score. Safety was analyzed at all follow-up visits and was reported individually for each study as well as for any exposure to sertraline in the program.

Results: Using a mixed model analysis, adolescents treated with sertraline had a significantly lower CDRS-R score compared with placebo-treated subjects ($p=0.012$). After 10 weeks of treatment, the difference in CDRS-R scores in children treated with sertraline trended toward significance ($p=0.053$). At open-label endpoint, compared to both the double-blind and open-label baselines, the improvement in CDRS-R scores was statistically significant in both age groups ($p<0.001$). 27.9% of children treated with sertraline in the double-blind studies discontinued for any reason, compared with 10.2% of placebo-treated subjects; equivalent proportions of adolescents discontinued from the double-blind studies in each treatment group (sertraline, 21.4%; placebo, 19.8%). In the open-label extension study, 42.1% of children discontinued for any reason compared with 33.3% of adolescents. Most adverse events were noted within 10 weeks of treatment onset. The most commonly observed adverse events in children treated with sertraline (at least 5% incidence and twice placebo) were insomnia, diarrhea, anorexia, vomiting, agitation, urinary incontinence, and purpura; and, in adolescents, diarrhea and vomiting.

Conclusion: With treatment up to 34 weeks, sertraline is effective in both children and adolescents with MDD, though, not surprisingly tolerability is better in adolescents.

Source of Funding: Supported by Pfizer.

Session II – 51

Validity of Patient Administered ADHD RS to Rate Adult ADHD Symptoms

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Background: Attention Deficit Hyperactivity Disorder (ADHD) is a common and impairing neuro-psychiatric disorder. ADHD symptoms are commonly classified by the ADHD Rating Scale (ADHD RS). The ADHD RS, an 18 item scale (based on DSM-IV criteria), rates symptoms 0-3 based on severity and frequency. Rater administration of the ADHD RS has been well standardized. The ability of patients to self-administer the ADHD RS is less well established. Also, the combination of frequency and severity ratings can be confusing to patients. We now present data regarding the concurrent validity of a clinician administered ADHD RS versus a frequency based, patient administered version of the scale. The self-administered ADHD RS is similar to the standard ADHD RS, with modifications in language and scoring the frequency of symptoms (0-4) ("never", "rarely", "sometimes", "often", "very often").

Methods: Patients seen in adult ADHD programs (NYU and Massachusetts General Hospital) for new evaluation or ongoing treatment were evaluated. All patients were diagnosed with adult ADHD by semi-structured clinical interview (childhood symptoms: ADHD module of K-SADS). Patients took the self-administered ADHD RS and then raters administered the standard ADHD RS. Internal consistency of symptom scores on each scale was assessed by Cronbach's alpha. Agreement of raters was established by intra-class correlation coefficients (ICCs) between scales.

Results: To date 60 patients have been evaluated. Their mean age was 37.5 $\pm$ 10.3 SD years. 68% were male, 85% had been diagnosed previously with adult ADHD and 77% were currently on medication. Internal consistency was high for both patient and rater administered versions, with Cronbach's alpha 0.88, 0.89, respectively. The ICC between scales for total scores was also high (0.84); ICCs for hyperactive-impulsive and inattentive symptom scores were also high (both 0.83) and we found substantial agreement for individual items (% agreement: 43%-72%) and significant kappa coefficients for all items ($p<0.001$).

Conclusions: This self-administered modified ADHD RS is a reliable and valid scale for the evaluation of ADHD adults. It is highly internally consistent and has high concurrent validity with the standard rater administered ADHD RS. Additional patient data will be included at the time of presentation as this is an ongoing trial. Item by item comparisons will also be elaborated.

Source of Funding: Educational Grant from Eli Lilly and Company

Session II – 52

Comparative Efficacy of Two Long-Acting Formulations of Methylphenidate and Placebo

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Objectives: To compare the pharmacodynamic profiles of (dl)-threo-methylphenidate (MPH) in two modified-release formulations, used in the treatment of ADHD; Ritalin®LA (20 mg) to Concerta® (18 mg), and Concerta® (36 mg). Twenty-nine male, and 7 female children, aged 6-12, with ADHD (C-DISC4 criteria), previously stabilized on MPH, completed this four-way crossover study. Subjects were observed over an 8 hour day in an analog (clinical) classroom (mimicking a community classroom). On Day 1 subjects visited the analog classroom for a 'Practice' visit. On Day 7, subjects received one of three treatments or placebo. On Days 14, 21, and 28, subjects received subsequent treatments. Days between treatments, subjects resumed medication for ADHD. In the classroom, the following assessments were completed: vital signs, SKAMP ratings and math tests. The primary objective compared the pharmacodynamic profile of Ritalin®LA 20 mg versus Concerta® 18 mg, for $AUC_{(0-4)}$ change from pre-dose in SKAMP-Attention ratings. The secondary objective compared the pharmacodynamic profile of Ritalin®LA vs. Concerta® 36 mg. The mean SKAMP attention pre-dose score for both the Ritalin®LA and Concerta® 18 mg treatments, was 1.6. The mean $AUC_{(0-4)}$ change from pre-dose for Ritalin®LA was -2.48 compared to –1.36 for Concerta® 18 mg (p=0.015), and to –1.55 for Concerta® 36 mg (1-sided p=0.021), showing that Ritalin®LA had a statistically greater effect on attention scores compared to both Concerta® 18 mg and 36 mg over the first 4 hour period. Similarly, Ritalin® LA showed statistically greater reduction in SKAMP deportment $AUC_{(0-4)}$ scores over the first four hours compared to both Concerta® 18mg an Concerta 36mg. All three active treatments were statistically significantly superior to the placebo treatment for SKAMP attention and behavioral ratings, and math-test attempted and correct scores. All treatments were well tolerated with similar rates and types of side effects being reported.

Source of Funding: Novartis Pharmaceuticals Corporation

Session II – 53

Modafinil Improves ADHD Symptoms in Children

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Introduction: In patients with ADHD, dysfunction of frontal-subcortical pathways may be an underlying cause of deficits in executive functioning. The wake-promoting agent modafinil acts selectively through the areas of the brain that regulate sleep and wakefulness to activate the frontal cortex.[1] In an open-label study, modafinil was shown to improve ADHD symptoms in children.[2] This study assessed different dose regimens of modafinil in children with ADHD. Results of different dose regimens of 300 mg/day modafinil are reported.

Methods: After a 1-week placebo washout period, children with moderate-to-severe ADHD were randomized to receive 4 weeks of treatment with placebo; 300 mg modafinil (as a single 300-mg morning dose or in split morning/midday doses of 100/200 mg or 200/100 mg); or 400 mg modafinil (in a split morning/midday dose of 200/200 mg). Randomization called for equal distribution of children by weight, except for the 200/200-mg arm, which contained only children ≥30 kg. Data from the 4 treatment groups with similar weights (placebo and 300-mg dose groups) are reported. Efficacy measures included the Teacher- and Parent-Completed ADHD Rating Scales.

Results: Of the 248 children enrolled, 198 were randomized to the placebo and three 300-mg modafinil treatment groups (average age, 9 y; average weight, 35.5 kg). Modafinil 300 mg given once daily significantly improved ADHD symptoms at school and home, as demonstrated in the total scores and inattentive and hyperactivity-impulsive subscale scores on the Teacher- and Parent-Completed ADHD Rating Scales ($P < .05$). Modafinil was well tolerated. Adverse events occurring in ≥10% of patients and more frequently with modafinil than placebo were insomnia, abdominal pain, anorexia, cough, fever, and rhinitis. Modafinil had no clinically significant effects on laboratory values.

Conclusion: Modafinil 300 mg once daily significantly improved ADHD symptoms in children and was well tolerated.

Source of Funding: Cephalon, Inc.

References:

1. Scammell TE, et al. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *J Neurosci* 2000;20:8620-8628.
2. Rugino TA, et al. Effects of modafinil in children with attention-deficit/hyperactivity disorder: an open-label study. *J Am Acad Child Adolesc Psychiatry* 2001;40:230-235.

Session II – 54

Citalopram Treatment of Pediatric Recurrent Abdominal Pain and Comorbid Internalizing Disorders: An Exploratory Study

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Objective: To assess the potential efficacy, acceptability, and safety of citalopram, a highlyselective serotonin reuptake inhibitor, in the treatment of functional pediatric recurrent abdominal pain (RAP) and comorbid internalizing disorders via an open label study in a clinically referred sample. RAP is a common presentation in pediatric settings, and has been associated with high rates of comorbid anxiety and depressive disorders.

Methods: Fifteen children and adolescents with functional RAP aged 7 to 18 years, inclusive, clinically referred from specialty gastroenterologic and primary care practices were entered in a 12-week open-label trial of citalopram following informed consent. Treatment was begun at 10 mg per day, increasing to 20 mg per day during week 2. Depending on clinical response, the dose could be increased to 40 mg per day at week 4 or reduced if side effects were reported. Primary outcome measure was the Clinical Global Impression Scale - Improvement (CGI-I), a seven-point clinician rated measure, with clinical responders achieving ratings of 1 (very much improved) or 2 (much improved). Secondary measures included self and parent reports of pain, anxiety, depression, and functional impairment. Side effects were assessed using a standardized checklist. Data were analyzed using an intent-to-treat format and the last measurement carried forward procedure.

Results: Thirteen subjects (87%) were classified as responders (CGI-I $\leq$ 2) and two (13%) as non-responders. Citalopram was generally well tolerated, but one subject withdrew prematurely due to reported visual side effects and another due to transportation problems. Child and parent ratings of abdominal pain, other somatic symptoms, anxiety, depression, and functional impairment improved significantly over the course of the study compared to baseline. Twelve subjects (80%) met criteria for an anxiety disorder and nine (60%) met criteria for a depressive disorder at study entry, but only four subjects (27%) continued to meet full criteria for either anxiety or depression at week 12. Reductions in pain and impairment were correlated with decreases in anxiety and depressive symptoms.

Conclusion: Citalopram is a promising treatment for functional pediatric RAP and deserves additional study via a randomized, placebo controlled clinical trial.

Source of Funding: Forest Laboratories, Inc.

Session II – 55

Quality of Psychopharmacologic Treatment for Children and Adolescents in "Real-World" Psychiatric Practice

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Objectives: 1) To assess quality of psychopharmacologic treatment for child and adolescent patients with Attention-Deficit/Hyperactivity Disorder (ADHD), Major Depressive Disorder (MDD), and Psychotic Disorder (PD) treated by psychiatrists; 2) to examine factors associated with the provision of quality care; and 3) to inform a larger scale study to assess patterns, quality and outcomes of psychopharmacologic treatment.

Methods: This study examined psychiatrist-reported cross-sectional clinical data for a national sample of 392 psychiatric patients under 18 years of age from the 1997 and 1999 APIRE Practice Research Network (PRN) *Study of Psychiatric Patients and Treatments (SPPT)*. Patients were systematically selected by psychiatrists participating in the APIRE PRN. Data is weighted to provide nationally representative estimates. 46% of the patients were diagnosed with ADHD (n=180), 17% MDD (n=67), and 20% PD (n=79) including Schizophrenia, Bipolar Disorder and Major Depressive Disorder with Psychotic Features. In this study quality of psychopharmacologic treatment has been defined by rates of concordance between psychiatrists' reported treatment and the American Psychiatric Association (APA) evidence-based quality indicators developed by the APA Task Force on Quality Indicators for Children.

Results: Findings indicate that consistent with the recommended care, 71% of children with ADHD received psychostimulants. 50% of patients with PD received antipsychotic treatment; however only 39% of PD patients received an atypical antipsychotic medication, as recommended. The overall rates for antidepressant treatment among patients with MDD were 83%, but only 56% received an SSRI as recommended. Factors such as patients' clinical and demographic characteristics, health plan type, treatment setting, and psychiatrists' training were associated with quality care, although factors influencing quality of care varied by disorder type.

Conclusion: There is considerable variation in rates of concordance with recommended care by diagnosis; a large proportion of patients with Psychotic Disorders received treatment not concordant with recommended care. Given the controversy surrounding use of antipsychotic medication for children, the treatment of Psychotic Disorders warrants considerable attention, including research on existing as well as novel treatments for this population. Although several factors were associated with the provision of quality care, reasons for non-conformance with evidence-based quality indicators need further exploration. Findings of this study will inform longitudinal clinical effectiveness studies with larger sample sizes to examine patterns, quality and outcomes of psychopharmacologic treatments.

Sources of Funding: The John D. and Catherine T. MacArthur Foundation; the American Psychiatric Foundation; the Center for Mental Health Services; and the Center for Substance Abuse Treatment

Session II – 56

Remission of Pediatric Social Anxiety Disorder with Paroxetine

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Background: Paroxetine (PAR) has been shown to effectively reduce the symptoms of social anxiety disorder (SAD) in children and adolescents. Recently, increasing importance has been given to achievement of remission of anxiety disorders.

Method: Data from the PAR pediatric SAD study were retrospectively analyzed to determine remission rates. The Intent-to-Treat (ITT) population in this double-blind, placebo-controlled, 16-week study consisted of 319 children (8-11 years, n=91) and adolescents (12-17 years, n=228) randomized to PAR (n=163) or placebo (n=156).

Results: At the Week 16 LOCF endpoint, the proportion of patients randomized to PAR who were in remission according to the criterion of a ≥ 70% reduction (from baseline) in Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA) total score was statistically significantly greater than for patients receiving placebo (47.2%, 75/159, vs. 13.3%, 20/150, respectively; adjusted odds ratio: 6.05; 95% CI:[3.38, 10.82]; $p<0.001$). Similarly, the proportion of PAR treated patients who achieved remission according to a criterion of Clinical Global Impression (CGI) Global Improvement score = 1 (very much improved) was also significantly higher than for placebo (47.8%, 77/161, vs. 14.9%, 23/154, respectively; adjusted odds ratio: 5.44; 95% CI:[3.09, 9.57]; $p<0.001$).

Conclusion: After 16 weeks of therapy, PAR treatment led to a statistically significant proportion of patients achieving remission from their social anxiety disorder symptoms, whether assessed using a disorder-specific measure (LSAS-CA change) or more general criteria (CGI-I=1).

Source of Funding: GlaxoSmithKline

Session II – 57

An Investigation of Factors Contributing To the Treatment-Seeking Behavior of Families of Children with Attention-Deficit/Hyperactivity Disorder

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Despite the high prevalence of Attention-Deficit/Hyperactivity Disorder (ADHD) in school-age children, approximately 50% of families with children with ADHD fail to pursue, or adhere to, recommended pharmacological or psychosocial treatments (Brown, Borden, & Clingerman, 1985; Firestone, 1982; Firestone & Witt, 1982). Recently, it has been suggested that attitudes towards the presenting problem and recommended treatments may play a role in initiation of, and adherence to, treatment for ADHD (Phelps, Brown, & Power, 2002). The present study is a prospective examination of the roles of treatment acceptability and perceptions of symptom severity in the pursuit of recommended treatments for ADHD.

The study sample was comprised of 60 families who attended an evaluation for ADHD at a major university-based medical center. During this evaluation, parent and child ratings of the acceptability of behavior therapy and medication were obtained using modified versions of the Abbreviated Acceptability Rating Profile (AARP; Tarnowksi & Simonian, 1992), and symptom severity ratings were obtained using the ADHD Rating Scale-IV (DuPaul et al., 1998). Parents also completed a demographic questionnaire and the Family Resource Scale (Dunst & Leet, 1987). The families were contacted three months later to obtain information regarding pursuit of treatment. A number of significant results were found. First, families who sought treatment endorsed greater resources and were more likely to be Caucasian than those who did not pursue treatment. Second, families who pursued treatment rated the child's ADHD as more severe than those who did not pursue treatment. Third, families who pursued medication had rated it as more acceptable than those families who did not pursue medication. Also, families who pursued monotherapy (behavior therapy or medication) rated their treatment choice as more acceptable than the alternative. These results suggest a significant relationship between acceptability of a treatment and subsequent pursuit of that treatment. Overall, these results have important clinical and research implications. By improving our understanding of how parents make important treatment decisions, we, as clinicians and researchers, can develop interventions to assist families in this process so that their ADHD child receives the most appropriate and effective treatment available.

Source of Funding: In part by an American Psychological Association Dissertation Research Award

Session II – 58

Long-Term Treatment of Generalized Social Anxiety Disorder with Venlafaxine XR

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Introduction: This double-blind study evaluated the efficacy, safety, and tolerability of venlafaxine extended release (XR) compared with placebo in long-term treatment of generalized social anxiety disorder (SAD).

Methods: In this study, 395 adult outpatients at 19 clinical centers were randomly assigned to receive 1 of 2 doses of venlafaxine XR (a fixed dose of 75 mg/day or a flexible dose of 150 to 225 mg/day) or placebo for up to 28 weeks. The primary efficacy variable was the Liebowitz Social Anxiety Scale (LSAS) total score. Secondary efficacy variables included the Clinical Global Impressions Improvement and Severity Scales (CGI-I, CGI-S), the Social Phobia Inventory (SPIN), and responder status (CGI score ≤ 2).

Results: The venlafaxine XR-treated patients demonstrated significantly greater improvement than the placebo-treated patients from weeks 2 through 28 on the CGI-I and from weeks 4 through 28 on the LSAS, CGI-S, and SPIN ($P<0.05$). There was a significantly greater proportion of responders in the venlafaxine XR group than in the placebo group at weeks 4 through 28 (58% vs 33%; $P<0.001$ at week 28). Venlafaxine XR treatment was generally well tolerated; adverse events included headache, nausea, nervousness, and somnolence.

Conclusion: These results demonstrate the efficacy and safety of venlafaxine XR in the long-term treatment of generalized SAD.

Source of Funding: Wyeth Research

Session II – 59

Oral Morphine in Treatment Resistant Obsessive Compulsive Disorder

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Method: We are conducting a placebo-controlled, double-blind trial to test the hypothesis that once weekly oral morphine is effective in treatment-resistant OCD. We recruited subjects with OCD for 3 years, who had failed at least 2 adequate SRI trials, and had Y-BOCS scores > 21. Current medications were continued. Subjects were randomized to random order, two-week blocks of once-weekly oral morphine sulfate, beginning at 30 mg; lorazepam, beginning at 1 mg; or placebo. The medication was administered in the clinic. Week 2 dosage was increased, decreased, or maintained depending on response and side effects.

Results: The first nineteen subjects, 14 men and 5 women, had a mean age (SD) of 39.8 (7.7), and had OCD for at least three years. They had failed from three to six SRI trials (mean = 3.3). The median Y-BOCS score at screening was 28.0 (range 20 to 38). After the highest morphine dose, the median Y-BOCS score was 24 (range 12 to 34) and the median decrease was 12.9% (range -70% to +43%). Six of the nineteen subjects were responders to morphine, with decreases in Y-BOCS score > 25%. In contrast, after the highest lorazepam dose, the median Y-BOCS score was 27 (range 15 to 33), and the median decrease was 6.2% (range -14% to +27%). Two subjects responded to lorazepam; one subject's Y-BOCS score decreased by 27% (compared to by 41% with morphine) and one by 25% (compared to by 70% with morphine). With placebo, the median Y-BOCS after the highest dose was 28, and the median decrease was 6.5%. No subject had a Y-BOCS decrease of >25%; one subject's Y-BOCS score increased 55%.

A Friedman two-way analysis of variance was significant (cr2 = 13.20, >p=.01) as was a Wilcoxon matched-pairs signed-ranks test for morphine vs. placebo (T=30.5, p=.015) but not for lorazepam. Several morphine responders maintained response for more than a year on twice weekly oral morphine without tolerance, euphoria, or drug seeking.

Discussion: Our results support the hypothesis that once- to twice-weekly doses of oral morphine can reduce symptoms in treatment-resistant OCD without creating tolerance or drug seeking behavior. Stimulation of mu-opoid receptors accelerates dopaminergic transmission in the striatum (Pieopponen et al., 1999) and inhibits glutamate release in cortical slices (Marek and Aghajanian, 1998). Most interestingly, acute stimulation of mu-opoid receptors disinhibits serotonergic neurons in the midbrain dorsal raphe nucleus by suppressing inhibitory GABAergic neurotransmission (Jolas et al., 2000). This could increase serotonergic tone in the basal ganglia and elsewhere just as does treatment with an SRI.Why some OCD sufferers are poorly responsive to treatment with SRIs or responsive to oral morphine is unknown.

Conclusion: Once-weekly oral morphine can substantially ameliorate OCD symptoms in some patients. Further research is indicated.

Source of Funding: National Center for Research Resources (NCRR) and Stanford University

Session II – 60

Remission Rates in Elderly Depressed Patients Treated with Sertraline

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Purpose: Depression in older adults is common, under-diagnosed, disabling, and treatable. Although increasingly recognized as an important indicator of antidepressant efficacy, little data is available on remission rates from placebo-controlled trials in the elderly. We report remission rates based on analyses performed on the largest placebo-controlled trial conducted in elderly patients with depression.

Methods: Outpatients (N=752) 60 years or older (mean age 69.9), with DSM-IV diagnosis of major depression, and a 17-item Hamilton Rating Scale for Depression (HAM-D) total score $\geq$ 18, were randomized to receive sertraline or placebo for 8 weeks. Remission was defined as endpoint HAM-D<10 or CGI-S of 1 or 2 (normal, not at all ill, or borderline mentally ill). Remission rates were calculated using the Cochran-Mantel-Haenszel Test.

Results: There were significantly more remitters in the sertraline group than in the placebo group. HAM-D remitters were 34% on sertraline and 24% on placebo (completers) and 29% on sertraline and 23% on placebo (LOCF at endpoint). CGI-S remitters were 37% on sertraline and 25% on placebo (completers) and 33% on sertraline and 23% on placebo (LOCF at endpoint).

Conclusion: These results suggest that sertraline is effective in achieving complete remission of symptoms in elderly patients with major depression. The 8 week duration of the study should be taken into account when interpreting these findings as longer antidepressant treatment periods, particularly in the elderly, may be associated with higher remission rates. Future studies are needed to confirm these observations.

Source of Funding: Pfizer**,** Inc.

Session II – 61

Mirtazapine Versus Paroxetine in Elderly Patients with Anxious Depression

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Background: To evaluate and compare the efficacy and safety of mirtazapine vs. paroxetine in patients ≥ 65 years of age with anxious major depressive disorder (MDD).

Methods: Subjects were drawn from a larger sample of 255 outpatients 65 years of age or older participating in an 8-week, double blind study comparing the efficacy and safety of mirtazapine (15-45 mg/day) with paroxetine (20-40 mg/day). Subjects met DSM-IV criteria for mdd and had a baseline ham-d 17 score ≥ 18 and an mmse score above the lowest 25th percentile. Only patients who also met criteria for anxious depression (Ham-D 17 anxiety/somatization factor score > 6) were included. Assessments for efficacy and safety were obtained throughout the duration of the study (baseline, day 7, 14, 21, 28, 42, and 56).

Results: Mirtazapine-treated patients (n=86) demonstrated comparable baseline demographics to patients receiving paroxetine (n=78). Based on LOCF two-way ANOVA analyses, mirtazapine-treated patients experienced a significantly ($p \leq .05$) greater reduction in depressive symptoms (assessed as actual Ham-D 17 score) than paroxetine-treated patients at Days 7, 14, and 21, while the two treatment groups did not differ significantly at Days 28, 42, and 56. Remission rates (a Ham-D 17 score ≤ 7) were significantly ($p \leq .05$) higher among mirtazapine-treated patients than among paroxetine treated patients at Day 14 (12.8% vs. 1.3%), but were not significantly different during the subsequent visits, including Day 56 (37.2% for mirtazapine and 30.8% for paroxetine). Both treatments appeared to be well-tolerated with fewer discontinuations due to adverse events in the mirtazapine-treated group.

Conclusions: Both mirtazapine and paroxetine were shown to be effective and well-tolerated in elderly MDD patients with anxious depression, although mirtazapine was associated with a more rapid onset of efficacy compared with paroxetine.

Source of Funding: Organon Pharmaceuticals, Inc.

Session II – 62

Neuroprotection as a Possible Mechanism of Antipsychotic Drug Action: A Role Of 5-HT_2 Receptor Blockade

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Nerve cell loss has been implicated in early onset schizophrenia (Thompson et al. 2001) and epidemiological studies point to a neuroprotective role of estrogen in this illness. Together these findings argue that nerve cell susceptibility to injury may be an important determinant of schizophrenia onset and severity (Seeman, 1997) and underscore the potential therapeutic value of neuroprotective strategies. Although preliminary studies suggest that novel antipsychotics such as risperidone and quetiapine could be neuroprotective in some models (Bai et al., 2002) neuroprotective properties of olanzapine (OLZ) have not been systematically studied. We used organotypic hippocampal cultures prepared from 7-12 day old Wistar rats to examine OLZ effects on neuronal survival in naïve and NMDA-treated cultures. After 2 weeks of culturing, slices were transferred for 1 week into the medium with added OLZ (0.01-10 μM), 5-HT_2 antagonist ketanserin (0.1-1 μM) or saline (control). Neuronal death was induced following the drug treatment by adding 50 μM NMDA for 30 min. to the medium. Cell death indicator was propidium iodide (PI) uptake measured 24 h after the NMDA treatment using confocal microscopy. Comparison of PI uptake between the treatment groups revealed that OLZ significantly ($P<0.05$, t-test, n=10-12 cultures) reduced PI uptake in naïve cultures and in cultures treated with NMDA at 0.1 and 0.01 μM respectively. Ketanserin had a similar effect. These data suggest that prolonged exposure to low concentrations of OLZ increases nerve cell survival and reduces NMDA-induced cell death. These actions may involve 5-HT_2 receptor blockade.

Source of Funding: Eli Lilly and Company and VISN22 MIRECC.

References:

Thompson PM et al., PNAS, v. 98: 11650, 2001
Seeman MV, Am J Psychiatry, v. 154: 1641, 1997
Bai O et al., J Neurosci Res, v. 69: 278, 2002

Session II – 63

Definitive Evidence that Aripiprazole is a D_2 and 5-HT_{1A} Partial Agonist

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Objective: To provide alternative biochemical readouts to support published *in vitro* evidence that aripiprazole has a mechanism of action at D_2 and 5-HT_{1A} receptors distinct from other effective antipsychotic drugs.

Methods: The study used [^{3}H]arachidonic acid release and [^{35}S]GTPγS binding assays to estimate the *in vitro* functional profile of aripiprazole at cloned human D_{2L} and native rat hippocampal 5-HT_{1A} receptors, respectively.

Results: Aripiprazole displayed a potent, partial agonist activity ($pEC_{50} = 8.13 \pm 0.23$) in stimulation of [^{3}H]arachidonic acid release in CHO cells stably expressing cloned human D_{2L} receptors; this effect was blocked in a concentration-dependent fashion by the selective D_{2L} antagonist raclopride. In comparison, haloperidol, olanzapine, ziprasidone, clozapine, and risperidone did not stimulate D_2 receptor-mediated increases in [^{3}H]arachidonic acid release. Aripiprazole also stimulated [^{35}S]GTPγS binding to rat hippocampal membranes with a potent partial agonist profile. Ziprasidone, but not clozapine, risperidone, or olanzapine, displayed a similar potent, partial agonist profile to that of aripiprazole.

Conclusion: The present study provides additional biochemical evidence to support existing claims that aripiprazole is a potent, partial agonist at D_2 and 5-HT_{1A} receptors. Furthermore, the *in vitro* functional profile of aripiprazole at D_2 and 5-HT_{1A} receptors was distinct from all other antipsychotic drugs tested.

Source of Funding: Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc.

Session II – 64

Safety and Tolerability of Aripiprazole in Patients with Schizophrenia Stratified by Race

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Background: The objective of this study was to examine the safety and tolerability profile of aripiprazole in patients with different racial backgrounds.

Methods: Data from short-term placebo-controlled studies of aripiprazole for treatment of schizophrenia or schizoaffective disorder were pooled and analyzed after stratifying patients by race. Of the 1339 patients who participated in these trials, 715 were White, 427 Black, 135 Hispanic, 31 Asian, and 31 were classified as Other. The small number of patient in the Hispanic, Asian, and Other categories makes meaningful interpretation of their AEs relative to the other racial groups difficult.

Results: Generally, the safety and tolerability profile of aripiprazole in patient subgroups paralleled that in the overall patient population. The incidence of adverse events was low and similar to placebo in each racial group. For patients who received aripiprazole, the incidence of the EPS reported as an adverse event was higher among black patients than in white patients. However, other EPS-related adverse events (tremor and hypertonia) were reported less frequently in black patients than in white patient who received aripiprazole. The incidences of somnolence and insomnia were similar across all racial groups, while nausea and vomiting occurred with somewhat greater frequency among white patients than among black patients treated with aripiprazole. The efficacy of aripiprazole was similar in White and Black patients.

Conclusion: In summary, no clinically important differences in the adverse event profile among racial groups have been identified. Aripiprazole appears to have a favorable safety and tolerability profile in all patients regardless of race.

Source of Funding: Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc.

Session II – 65

Aripiprazole for Psychosis of Alzheimer's Disease

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Background: To evaluate the efficacy of aripiprazole in patients with psychosis of Alzheimer's disease.

Methods: In a 10-week, multicenter trial, 208 outpatients with psychotic symptoms associated with Alzheimer's dementia (mean age 81.5 y, baseline MMSE = 14.2, score ≥ 6 on NPI Psychosis subscale), were randomized to placebo or flexible doses of aripiprazole, initiated at 2 mg/day for 2 weeks, with option to increase dose up to 15 mg/day. Efficacy was assessed by Neuropsychiatric Inventory [NPI] Psychosis subscale and Brief Psychiatric Rating Scale (BPRS).

Results: Mean dose of aripiprazole was 10 mg/day. At week 10, NPI Psychosis score was improved with both aripiprazole and placebo (-6.55 vs –5.52, P=0.17). Patients treated with aripiprazole experienced an improvement in the BPRS Total score and a significant improvement in BPRS psychosis (hallucinations and delusions) subscore vs those treated with placebo (P=0.03). Discontinuation rates due to adverse events were 8% with aripiprazole and 7% with placebo. Somnolence was mild and not associated with falls or accidental injury. There were no significant differences in ECG abnormalities, vital signs, labs, or weight.

Conclusions: Aripiprazole improved symptoms of hallucinations and delusions in community-living AD patients with psychosis. Aripiprazole was safe and well-tolerated in this elderly population.

Source of Funding: Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc.

Session II – 66

Rivastigmine Treatment with Slow Titration Provides Early Behavioral Benefits in Mild to Moderately Severe AD

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Background: Alzheimer's disease patients frequently present with prominent behavioral disturbances causing significant distress for patients and caregivers. These behavioral symptoms are usually progressive and play a key role in the decision to institutionalize.

Methods: The behavioral efficacy of rivastigmine was evaluated in a 6-month, open-label, multi-center study employing a 4-week minimum titration schedule. 147 outpatients aged 50 to 85 (mean 75) with mild to moderately severe Alzheimer's disease of approximately 3 years' duration were enrolled. Following a minimum of 4 weeks at the initial dose of 1.5 mg capsules bid, patients were titrated to their highest tolerated dose, ≤12 mg/day. The behavioral assessment instrument was the NPI-12.

Results: Baseline mean NPI-12 score was 11.5. At 3 months, and prior to many patients having reached their maximum dose, preliminary analysis of the ITT population indicated a statistically significant improvement in NPI-12 scores compared to baseline. Improvement in behaviors at Month 3 was a mean change from baseline in total NPI-12 score of –1.9 points ($p=0.02$). Furthermore at Month 3, eight of the twelve individual symptom domains indicated improvement from baseline, including agitation/aggression, depression, apathy and irritability. Measures of cognition and global functioning also showed improvement from baseline at Month 3 (mean change in MMSE of + 0.1 point and mean CGIC rating of 3.6 points, respectively). Sustained behavioral and cognitive benefits were noted at Month 6.

Conclusion: These preliminary data indicate that most behaviors improve significantly and early in the course of treatment with rivastigmine. Measures of cognitive and global function were also improved at 3 months, and all efficacy measures indicated sustained benefits at Month 6.

Source of Funding: Novartis Pharmaceuticals Corporation

Session II – 67

Pharmacological Treatment of Dementia with Lewy Bodies (DLB): Preliminary Report from the International Psychogeriatric Association (IPA) Special Meeting on DLB

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Background: Dementia with Lewy bodies (DLB) has been a topic of great interest and controversy in recent years. In order to evaluate all the available information on the subject IPA sponsored a meeting of more than forty international experts in Budapest in November 2002. The meeting evaluated many aspects of knowledge relating to DLB and Parkinson Disease with dementia (PDD).

Methods: Panelists summarized available information on pharmacological treatments in DLB and PDD in several 10-minute presentations. Representatives of the United States Food and Drug Administration (FDA) and Health Canada (Canadian regulatory agency) addressed regulatory issues and opinion was also sought from Europe, Japan and Australia.

Results: There is emerging and consistent evidence that cholinesterase inhibitors (ChE-I) are efficacious in DLB. Whether they should be first choice of treatment in DLB in which patients are likely to respond, are open questions that need to be addressed. Adverse event profiles may differ from those seen in Alzheimer's disease (AD) but worsening of extrapyramidal motor features does not seem to be a clinically significant problem in this group. Future studies should assess all three domains of cognition, particularly attention, motor symptoms, function measures and neuropsychiatric features as well as including a global assessment of change measurement. The differential or synergistic effect of atypical antipsychotics and cholinesterase inhibitors should also be explored in this population.

Regulatory Issues:
- There are no current treatments for DLB or PDD that have regulatory approval
- Regulatory authorities seem prepared to accept DLB or PDD as an indication if
  a) Existence of these entities is generally accepted by the field of experts
  b) The disorders can be operationally defined by reliable and valid criteria
  c) Outcomes for studies use validated and standardized measures
- FDA has considered DLB as an indication and initially has suggested that there be dual primary outcomes of global and specified measure of cognition

Conclusion: Current available information suggests that DLB and PDD are important potential targets for therapeutic development. Specifically designed clinical trials are needed to fully evaluate the impact of current and emerging treatments in this population.

Source of Funding: The meeting was funded through the International Psychogeriatric Association, which itself received funding from Janssen Pharmaceutica Products LP, Johnson & Johnson Pharmaceutical Services LLC, Targacept Inc, AstraZeneca and Forest Laboratories Inc. Travel support to the meeting was provided by Janssen Pharmaceutica.

Session II – 68

Olanzapine Versus Placebo in the Treatment of Psychosis with or without Associated Behavioral Disturbances in Patients with Alzheimer's Dementia

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Introduction: Psychotic symptoms and behavioral disturbances are a major concern in the care of elderly patients with Alzheimer's dementia (AD).

Objective: To compare the efficacy of olanzapine versus placebo in patients with psychosis or behavioral disturbances associated with Alzheimer's dementia (AD) in long-term or continuing-care settings.

Methods: Inpatients with AD and delusions or hallucinations were randomly assigned to receive placebo or fixed-dose olanzapine (1.0, 2.5, 5.0, 7.5 mg/day) for up to 10 weeks of double-blind treatment.

Results: Mean age of patients (N=652) was 76.6 years; 75.0% were female. At endpoint, significant decreases from baseline in the NPI/NH Psychosis Total (*Delusions+Hallucinations*) were seen in all five treatment groups (p<.001). Repeated-measures analysis showed no significant differences among treatment groups at the 10-week endpoint, but LOCF (last-observation-carried-forward) decreases in the 7.5-mg olanzapine group were significantly greater than placebo (p=.008), and median time to response (≥30% improvement in Psychosis Total) was significantly shorter (15.0 versus 29.0 days, p=.020). Changes in extrapyramidal measures and cognition were not significant in any treatment group. No treatment-emergent adverse events occurred with a significantly higher incidence in any olanzapine group relative to placebo. Mean changes from baseline in glucose, triglyceride, and cholesterol levels were not significantly different across groups, and no clinically relevant significant changes were seen across groups in any other vital sign or laboratory measure.

Conclusions: These data indicate that olanzapine at 7.5 mg/day is well tolerated and effective for psychotic symptoms associated with AD.

Source of Funding: Eli Lilly and Company

Session II – 69

Meta-Analysis of Atypical Antipsychotics for Dementia Patients: Balancing Efficacy and Adverse Events

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Abstract: Antipsychotics comprise the bulk of long-term care prescriptions for psychotropic drugs. Over the past decade atypical antipsychotics have largely replaced conventionals in this area. Yet this is an off-label use and there are few clinical trials of atypicals in this population. We conducted independent systematic reviews (i.e., meta-analyses) of atypical antipsychotics and haloperidol trials in people with dementia in order to better understand their methods and limitations and to quantify, where possible, evidence for efficacy, extent of adverse events, and estimate effectiveness. Previous work has not dealt with this systematically or quantitatively, has been company-sponsored limited analyses, or antedated the atypical trials.

Methods: Established methods were used for searching and abstracting materials (Cochrane, 2002). Randomized, placebo-controlled, double blind clinical trials of atypicals and haloperidol - when compared to atypicals - were selected. ITT outcomes were combined, and effect sizes calculated using standard techniques and expressed as standardized mean differences, d, and rate differences (Borenstein et al 2002). In addition, deaths across all antipsychotics, and cerebrovascular events within the risperidone trials were assessed.

Results: The following reported trials were identified: 3 risperidone in nursing homes: 2 olanzapine; one each quetiapine and tiapride; and 3 haloperidol comparisons. Unreported and ongoing trials were identified as well. Inclusion criteria varied from only patients with AD to allowing other dementia, as did critical symptoms from requiring only mild agitation to the presence of psychosis. Interventions were with fixed, adjusted, or individualized dosing of medications. Trial lengths were generally 10-12 wks (range, 3 to 12 wks). Outcomes included global impressions, rating scales, compliance and adverse event ratings. Risperidone and haloperidol contrasts allowed for statistical combining, the few trials reported for the other drugs allowed only for an assessment of selected adverse events.

839 NH patients were included in the risperidone, 1 mg/d contrasts. Patients had agitation or aggression, not necessarily psychosis; about 70% had AD and 22% had vascular dementia; trials were 12 wks. Risperidone had clear incremental effects over placebo for clinical scale change and for 30% improvement (0.23 d, 95% CI [0.10, 0.37] and 0.13 rate difference [0.01, 0.24]). The modest effects were attenuated somewhat by non-completion in both groups and accumulated serious adverse events in this medically compromised population. The single 2 mg/d fixed dose comparison markedly increased adverse events, to the extent of negating overall effectiveness compared to 1 mg/d. There was a trend for deaths to be associated with randomization to any antipsychotic. Individual patient meta-analyses are needed as well as significant changes to clinical trials methods in order to better assess effectiveness, in contrast to efficacy, of these drugs in dementia.

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Efficacy and Tolerability of Memantine in Nursing Home Patients with Moderate-to-Severe Dementia of the Alzheimer's Type

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Background: Memantine, a voltage-dependent, moderate-affinity, uncompetitive NMDA-receptor antagonist, is efficacious, safe, and well-tolerated in treating nursing home patients with moderate-to-severe dementia, including both dementia of the Alzheimer's type (DAT) and vascular dementia (VaD)(Winblad, 1999). Further analyses of the DAT subpopulation were conducted.

Methods: This was a 12-week randomized, double-blind, placebo-controlled study. Nursing home patients with dementia (DSM-III-R diagnostic criteria) were randomized to receive either placebo or memantine 10 mg/day, administered orally once daily. Patients were subgrouped by dementia types using the modified Hachinski Ischemia Scale into the DAT (score ≤4) or VaD (score >4) subpopulations. Efficacy measures included the Clinical Global Impression of Change (CGI-C)(global effects), the Behavioral Rating Scale for Geriatric Patients (BGP) care-dependency subscale (functional effects) and the BGP cognitive subscale (cognitive effects) and were analyzed using the last observation carried forward (LOCF) and observed case (OC) approaches. Safety/tolerability was assessed by monitoring adverse events, electrocardiograms, vital signs, and laboratory tests.

Results: Of 166 randomized patients, 79 were diagnosed with moderate-to-severe DAT (mean baseline MMSE score 6.7-6.8). Memantine-treated DAT patients showed significantly greater improvement than placebo-treated DAT patients on the CGI-C scores, BGP care-dependency subscores, and the BGP cognitive subscores ($p \leq 0.01$). Significant treatment effects at Week 12 confirmed the superiority of memantine over placebo using both the LOCF and the OC approaches ($p \leq 0.01$). Adverse events were similar in both groups with no clinically important changes in vital signs or laboratory parameters.

Conclusions: Memantine 10 mg/day is safe and well-tolerated, and on the basis of global, functional, and cognitive outcome measures, provides significant improvement for patients with moderate-to-severe dementia and more specifically for patients with DAT in a nursing home environment.

Source of Funding: Forest Laboratories, Inc. and Merz Pharmaceuticals, GmbH.

Reference:

Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-best study (benefit and efficacy in severely demented patients during treatment with memantine). *International Journal of Geriatric Psychiatry* 1999;14:135-146

Session II – 71

Memantine/Donepezil Dual-Therapy is Superior to Placebo/Donepezil Therapy for Treatment of Moderate to Severe Alzheimer's Disease

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The only treatments for Alzheimer's disease (AD) approved in the US are cholinesterase inhibitors (ChEIs). The moderate-affinity, uncompetitive NMDA receptor antagonist memantine represents a novel therapy for AD in the US, and is currently approved for this indication in Europe. Memantine monotherapy has been shown in multicenter placebo-controlled trials to be effective and well tolerated in AD patients, but there are no data addressing combination therapy. We conducted a 24-week, double blind, parallel arm, placebo-controlled trial at 37 US centers in patients with moderate-to-severe AD also treated with stable doses of the ChEI, donepezil. Inclusion criteria were: diagnosis of probable AD by NINCDS-ADRDA criteria, Mini-Mental State Exam (MMSE) score of 5-14, MRI or CT scan consistent with the diagnosis of probable AD, and daily donepezil therapy for the past 6 months (stable dose for the past 3 months). Primary outcome assessments were the Severe Impairment Battery (SIB), a performance-based measure of cognition, and the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) inventory, a measure of daily function. A physician's global assessment, the Clinician's Interview-Based Impression of Change-Plus (CIBIC-Plus) was also performed. Statistical analyses were performed on the ITT population using an LOCF approach.

Of the 403 patients who were randomized and treated with memantine 10 mg b.i.d. (n=202) or placebo (n=201), 85% of memantine treated patients and 75% of placebo patients completed the trial. Mean MMSE at entry was 10. At week 24, patients treated with memantine and donepezil showed a statistically significant improvement ($p < 0.001$) in cognitive function (SIB) compared to patients treated with donepezil and placebo, and showed significantly less decline ($p=0.028$) in daily function (ADCS-ADL). A significant difference in favor of memantine/donepezil was also seen on the CIBIC-Plus global assessment ($p=0.027$). Memantine/donepezil treatment was safe and well tolerated. These results further support the safety and efficacy of memantine therapy for patients with moderate-to-severe AD and demonstrate that treatment with memantine combined with donepezil is superior to donepezil alone. Importantly, treatment with memantine/donepezil resulted in improved cognitive performance relative to baseline whereas treatment with donepezil alone was associated with continued cognitive decline.

Source of Funding: Forest Laboratories, Inc.

Session II – 72

Measuring and Treating Organizational, Time Management, and Planning Deficits in Children with AD/HD

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Background and Objectives: Treatments for major aspects of Attention Deficit/Hyperactivity Disorder (hyperactivity, impulsivity, and attention span) have been widely studied with resulting major advances in care. In contrast, there has been little effort to develop methods for treating the impact of AD/HD on deficits in organizing actions to complete tasks, planning actions to meet goals, and managing time in order to meet goals, behaviors known to be problematic in AD/HD and detrimental to academic functioning, family relationships, and life success. We aimed to fill this gap by developing valid and reliable methods for measuring organizational, time management, and planning skills in children, determining their distribution in a normative sample, and developing a method for treating such deficits.

Method: Teacher, parent, and child versions of the Children's Organizational Skills Scale (COSS) were created in consultation with teachers, clinicians, and research experts to reflect the day-to-day struggles that children with AD/HD have with organizing their actions for school and home tasks. Normative samples of third to eighth-graders included 915 children rated by teachers from regular classroom settings and 138 children who were rated by themselves and their parents. A 20-session, flexible individual treatment program was designed, using a three-pronged approach to teach materials and space management, time management, and planning for school and home tasks. A pilot study is currently testing this intervention. Children are monitored weekly, using the COSS, by teachers, parents, and therapists.

Results: The teacher version of the COSS had good reliability and internal consistency. Three factors measuring organized actions, materials management and memory, and task planning were extracted and shown to discriminate AD/HD from normative children. Definitive analyses of the Parent and Child Versions of the COSS await larger samples.

Conclusions: Children with AD/HD possess deficits in time management, materials management, and planning in the school setting. These deficits are not universal so care must be taken in assessing individuals and expending clinical resources to improve functioning. Intervention can be matched to deficits demonstrated in the school and home setting. That intervention warrants careful testing. Statistical complexities regarding the study design will be discussed.

Source of Funding: NIMH – R21

Session II – 73

A Naturalistic Comparison of Olanzapine and Risperidone in Children and Adolescents with Schizophrenia

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Background: Treatment modalities for early-onset schizophrenia include the use of pharmacologic agents, namely atypical antipsychotics. However, there have been few published studies regarding the safety of efficacy of these agents in children and adolescents. The purpose of this naturalistic study is to evaluate the short-term and long-term effectiveness of olanzapine and risperidone in children and adolescents with schizophrenia, schizoaffective disorder, or schizophreniform disorder.

Method: Children and adolescents, between the ages of four and 18 years and started on olanzapine (N=43) or risperidone (N=106) between July 1, 1995 and July 31, 2000, were considered for the study. Total, internalizing, and externalizing Child Behavior Checklist (CBCL) scores were analyzed at baseline, 90-day, 1-year, and 2-year periods utilizing repeated measures analysis of variance. Two-year hospitalization rates and time to hospitalization were measured by the Kaplan-Meier formula. All statistical tests were two-tailed, and significance defined as an alpha less than 0.05.

Results: All groups had significant improvements in total and internalizing CBCL scores at 90-day, 1-year, and 2-year post baseline ($p<0.05$). Significant improvements in externalizing CBCL scores were observed only at 90-days. There were significant differences between treatment groups for total CBCL scores at 1-year ($p=0.034$), and for internalizing CBCL scores at 1 and 2-year post baseline ($p<0.05$). There were no differences in externalizing CBCL points during the 2-year period. There was no significant differences in 2-year hospitalization rates, but a significant difference in time to hospitalization for the risperidone group when compared to the olanzapine group ($p=0.015$).

Conclusions: Olanzapine and risperidone were effective in children and adolescents with schizophrenia, schizoaffective disorder, or schizophreniform disorder in reducing total and internalizing CBCL scores at all time points. There was no significant improvement on externalizing CBCL scores for both groups. Patients receiving risperidone had lower total CBCL scores at 1-year, and lower internalizing CBCL scores at 1 and 2-year post baseline. Additionally, the risperidone group had longer time to hospitalization compared to the olanzapine group.

Source of Funding: Research funded in part by the Texas Department of Mental Health and Mental Retardation.

Session II – 74

The Treatment of Schizophrenia in Routine Psychiatric Practice

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Objectives: 1) Characterize treatment patterns for adult psychiatric patients with schizophrenia; 2) Assess conformance with the Schizophrenia Patient Outcomes Research Team (PORT) guideline recommendations.

Methods: Nationally representative data from the *1999 APIRE Practice Research Network Study of Psychiatric Patients and Treatments* were used to examine treatment for 284 systematically selected patients with schizophrenia and schizophrenia spectrum disorders.

Results: Most patients were clinically complex: 68% had a comorbid Axis I, II or III disorder and 32% had a comorbid substance disorder. 80% received two or more medications; 56% 3 or more. 94% of patients received an antipsychotic (68% atypical); 43% benzodiazepine/antianxiety; 38% antidepressants. 36% had medication side effects and 39% had treatment compliance problems. 48% received psychotherapy and 63% received some form of psychosocial treatment. Although guideline conformance rates were higher for psychopharmacologic than psychosocial recommendations, rates varied considerably. For example, 95% of the patients with comorbid depression received an antidepressant; however, only 20% of the patients with treatment compliance problems received a depot antipsychotic.

Conclusions: Most patients received multiple psychopharmacologic treatments. A significant proportion did not receive guideline consistent treatment. Longitudinal research that includes an assessment of treatment effectiveness is needed to determine if there is an empirically based clinical rationale for deviating from established treatment guidelines.

Source of Funding: Development and support of the PRN has been generously funded by the John D. and Catherine T. MacArthur Foundation, the American Psychiatric Foundation, the Center for Mental Health Services and the Center for Substance Abuse Treatment.

Session II – 75

Meta-Anaylysis of the Efficacy of First- and Second-Generation Antipsychotics

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Objective: We performed a meta-analysis from randomized trials comparing second-generation with first-generation antipsychotics and those comparing second-generation antipsychotics to examine efficacy differences.

Methods: Ten second-generation antipsychotics were examined in a meta-analysis of 150 randomized, controlled trials: 127 studies comparing a second-generation with a first-generation (or conventional) antipsychotic, and 23 studies comparing different second-generation drugs. We searched the literature for trials from 1953 to December 2002 of schizophrenia patients from electronic databases, reference lists, posters, the Food and Drug Administration, and other unpublished data. For evaluation of data extraction, we compared our effect sizes with effect sizes we calculated from the N, mean, and SD from several existing meta-analyses.

Results: Analyses using Comprehensive Meta Analysis found that amisulpride, clozapine, olanzapine, and risperidone were more efficacious than first-generation antipsychotics with statistically significant effect sizes of 0.29 (0.18, 0.40), 0.48 (0.31, 0.65), 0.20 (0.13, 0.27), and 0.25 (0.18, 0.32) respectively. Remoxipride, zotepine, sertindole, quetiapine aripiprazole, and ziprasidone did not differ significantly from first-generation antipsychotics (note: a limited number of studies were available for the latter four drugs). Comparisons between clozapine versus olanzapine or risperidone did not show clozapine to be more efficacious. However, meta-regression of risperidone versus clozapine showed that clozapine dose was a statistically significant moderator variable ($p=0.008$), indicating that in comparisons using higher clozapine doses, clozapine tended to be more efficacious than risperidone.

Conclusion: Our results suggest that second-generation drugs differ from each other and should not be treated as a homogeneous group. We found clozapine, amisulpride, risperidone, and olanzapine to be more efficacious than first-generation antipsychotics.

Source of Funding: Academic institutional support

Session II – 76

Antipsychotic Polypharmacy in Ambulatory Settings: 8 Years of Data from the National Ambulatory Medical Care Survey

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Objective: The concurrent use of multiple antipsychotics in the same patient (antipsychotic polypharmacy) seems to be increasing and reportedly occurs in up to 30% of psychiatric inpatients. To characterize the prevalence of antipsychotic polypharmacy in the community, we analyzed 8 consecutive years of data from the National Ambulatory Medical Care Survey (NAMCS), an annual survey conducted by the Centers for Disease Control and Prevention (CDC). Factors associated with the presence of antipsychotic polypharmacy were identified using logistic regression.

Methods: National prevalence estimates for antipsychotic use and antipsychotic polypharmacy were calculated for each survey year using the methods developed by the CDC. Relative standard error (RSE) for the sample was 0.53%, well below the 30% maximum value established by the CDC. Logistic regression was used to compute odds ratios for the presence of antipsychotic polypharmacy for 11 exploratory variables.

Results: During the 8 year study period data were collected for a total of 232,439 physician office visits. Antipsychotics were reported in 2,368 (1%) visits. Of the 2,368 antipsychotic visits, 4.4% (N=104) were visits in which the patient was receiving more than one antipsychotic. Calculations of national prevalence estimates from these data indicate that over the 8 year period, the proportion of patients receiving antipsychotic polypharmacy was 5.1%. Logistic regression revealed 4 significant ($P<.05$) explanatory variables: year of office visit, diagnosis of schizophrenia, psychosis, or anxiety. The national prevalence of antipsychotic polypharmacy was computed for each year and, with the exception of one year (1995) increased each year. The 7.8% estimated prevalence in 2000 represents more than a three fold increase from 1993 (2.3%).

Conclusion: The prevalence of antipsychotic polypharmacy has significantly increased during the 8 year study period. The strongest predictor of polypharmacy was the year in which the patient visit occurred. The rate of polypharmacy in the community (7.8%) does not appear to be as high as that reported for psychiatric inpatients (25%).

Source of Funding: University of Kentucky College of Pharmacy

Session II – 77

Antipsychotic Maintenance in Schizophrenia: Partial Compliance and Clinical Outcome

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Objective: To evaluate clinical implications of continuous medication treatment for patients with schizophrenia.

Methods: In a multicenter trial, 565 chronic schizophrenia patients in acute exacerbation were randomized to receive risperidone or "best choice" conventional antipsychotics. Symptoms (PANSS total scores) were assessed at baseline and follow-up and medication compliance (defined as days of medication possession/outpatient days x 100) was calculated from patient records.

Results: Partial compliance was typical in these patients: 94% received no antipsychotic drug for varying periods (mean 112 days) and almost 50% had medication compliance of 70% or less. A regression model accounting for over 25% of the variance in the PANSS score indicated a 20% drop in compliance predicts a 3.1-point increase in PANSS total scores ($p < 0.001$). Improvements in PANSS scores were significantly greater in patients with higher compliance scores ($p < 0.001$). Controlling for compliance, a regression model indicated a 4.7-point or approximately 30% greater improvement in PANSS scores with risperidone than conventional agents ($p < 0.0026$).

Conclusion: The finding of a direct correlation between degree of partial compliance and clinical outcome emphasizes the importance of treatment strategies that promote continuous medication treatment with an atypical antipsychotic.

Source of Funding: Janssen Pharmaceutica Products, L.P.

Session II – 78

Review of the First Year of Inpatient Ziprasidone Use

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Background: Ziprasidone, a newer atypical antipsychotic introduced in February 2001, has comparable efficacy to and better tolerability than conventional antipsychotics. We reviewed ziprasidone use to assess clinical practice patterns, clinical status, and tolerability.

Methods: Inpatient medical records of patients admitted to McLean Hospital who received ziprasidone from March 2001 through February 2002 were reviewed. Data collected included dosing, presenting illness, diagnoses, concomitant psychotropics, clinical changes, adverse effects and EKG data.

Results: Ziprasidone was prescribed in 151 inpatients (3.4% of admissions; 108 women, 43 men) presenting with depression (N=56), psychosis (N=45), other (N=36), and mania (N=14). The initial mean dose was 50 ± 34 mg/day, final mean dose was 72 ± 46 mg/day, and mean dose at discharge was 83 ± 46 mg/day. Patients with DSM-IV diagnoses of schizoaffective disorder (N=45) had the highest mean change from initial to final dose, with a 61% increase. In 41 of 151 cases (27%), ziprasidone was the single antipsychotic at discharge. Ziprasidone was discontinued prior to discharge in 32% of cases, 17% due to lack of efficacy, 9% due to side effects, and 7% other/unreported. Sixty-nine subjects had EKGs performed after starting ziprasidone; eight had QTc >450 msec. EKG data was reported in 39 subjects (26%) before and after ziprasidone initiation without significant QTc change. Ziprasidone was discontinued in 4 patients due to concerns over QTc, three of whom had QTc >450 msec (460-479 msec). No patient had QTc >500 msec or an untoward outcome associated with prolonged QTc. Changes in baseline to discharge CGI and GAF scores were similar across diagnoses, and unrelated to length of stay and initial/final ziprasidone doses.

Conclusions: Ziprasidone was well tolerated, used in the treatment of affective as well as psychotic disorders, and should be studied in controlled trials in patients with diagnoses other than schizophrenia.

Source of Funding: Bruce J. Anderson Foundation and the McLean Hospital Private Donors Neuropsychopsychopharmacology Research Fund

Session II – 79

Long-Term Efficacy and Safety of Olanzapine and Haloperidol in First Episode Schizophrenia

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The aim of this study was to compare, in a large and well-controlled clinical trial, the acute and long-term effectiveness of olanzapine and haloperidol in first episode schizophrenia and schizoaffective disorder patients. 263 first-episode subjects were randomly assigned under double-blind conditions to haloperidol or olanzapine and followed for up to 104 weeks. Domains measured included treatment continuation and adherence, psychopathology, psychosocial measures, neurocognitive function, brain morphology and metabolism. Both haloperidol and olanzapine were associated with substantial and comparable reductions in symptom severity. At 12 weeks, olanzapine treated subjects showed significantly greater symptom decreases in mixed model analysis, lower rates of treatment-emergent Parkinsonism and akathisia and greater weight gain. Treatment discontinuation rates were high overall with only 47 patients remaining in the study by 2 years. Retention was greater with olanzapine. Beginning by week 6, there were more dropouts with haloperidol than olanzapine, and this difference in dropout rates widened over the course of the study with 12% of haloperidol subjects and 24% of olanzapine subjects staying in the study at two years. The psychopathology and safety results of through 104 weeks will be presented and discussed.

Source of Funding: Eli Lilly and Company

Session II – 80

The Effectiveness of Behavioral Treatment for Weight Loss in Patients with Schizophrenia

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Objective: To evaluate the efficacy of a group-based behavioral treatment for weight loss in overweight and obese patients suffering from schizophrenia.

Methods: Seventy-one overweight/obese patients (BMI>26) with DSM-IV schizophrenia or schizoaffective disorder were enrolled in 14-week multi-center weight reduction study. Patients were randomly assigned to either behavioral treatment (BT, n=35) or Usual Care (UC, n=37). The BT group received 20 group sessions focused on calorie intake reduction techniques. UC group patients received no guidance on weight reduction. Patients were weighed at baseline and 4-week intervals.

Results: Mean weight loss was numerically but not significantly higher in the BT versus the UC group (BT, –1.95$\pm$3.79kg; non-BT, –1.08 $\pm$3.11kg). In an intent-to-treat analysis, there was a trend for more BT patients to lose $\geq$5% of their body weight versus UC patients (36.0% vs. 16.0%, p=0.088). Six patients dropped out before receiving any BT. When all patients who completed at least one BT session were included BT was associated with a significantly higher proportion of patients with at least 5% weight loss (p=0.033).

Conclusion: This pilot study demonstrates that this behavioral treatment may be effective for weight reduction in overweight/obese patients with schizophrenia.

Source of Funding: Supported by Janssen Pharmaceutica Products, L.P.

Session II – 81

Long-Acting Injectable Risperidone: Safety and Efficacy in Stable Patients Switched from Conventional Depot Antipsychotics

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Objective: Long-acting injectable risperidone (Risperdal Consta™) was evaluated in symptomatically stable patients who had been receiving conventional depot antipsychotics.

Methods: In a 12-week, multicenter, open-label study, after a run-in period that included 2 cycles of their depot antipsychotic, patients were switched to long-acting risperidone given by intramuscular injection every 2 weeks.

Results: The mode dose of long-acting risperidone was 25 mg in 86% of the patients and 37.5 mg in 14%. The trial was completed by 92% of the patients. Adverse events were reported in 58% of the 166 patients, the most common being psychosis in 13%, insomnia in 10%, headache in 7%, and rhinitis in 7%. Hyperprolactinemia was reported in 11 % of the patients; however, no association between prolactin levels and any signs or symptoms known to be associated with hyperprolactinaemia was noted. Adverse events related to extrapyramidal symptoms (EPS) were reported in 5 patients (3%). Severity of EPS was low at baseline and was further reduced during the trial. At endpoint, significant improvements were seen in mean PANSS total scores and scores on the positive and negative subscales.

Conclusion: Long-acting injectable risperidone was well tolerated and efficacious in patients whose treatment was switched from conventional depot antipsychotics.

Source of Funding: Supported by Johnson & Johnson Pharmaceutical Research & Development

Session II – 82

Clozapine Use in Clinical Trials Vs. Real-World Settings

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Background: While a moderately high rate of response to clozapine has been shown in clinical research trials of people with treatment resistant schizophrenia (Lieberman, Kane 1994), response rates as reported in these research reports may differ from those seen in real-world practice settings (Essock, 2002).

Methods: Clinical trial data obtained from an inpatient treatment research unit were compared to real-world data obtained from the State of Maryland Clozapine Authorization and Monitoring Program Database (CAMP). Comparisons were made between age, race, sex, and BPRS scores for all patients treated in inpatient settings between 1992 and 2002.

Results: Clozapine-treated patients in the CAMP database had more negative symptoms ($p<0.001$), activation ($p<0.001$) and total BPRS scores ($p=0.013$) than those who were treated in the inpatient treatment research unit. Positive symptoms, other symptoms and ages between the two groups are similar. More females were entered into clinical trials than the percentage treated in the CAMP database ($p=0.028$) and a trend was noted for more non-black minorities to be treated in the CAMP database than on the clinical trial unit ($p=0.083$).

Conclusions: Differences in ability of people to consent for research studies and sampling differences may lead to important limits on the generalizability of findings from clinical trials involving the seriously mentally ill. This work provides evidence on the differences in patient characteristics and outcome in clinical trials versus real-world settings and may help explain differences in clozapine treatment outcome across different variables and settings.

Sources of Funding: Theodore and Vada Stanley Foundation and NIMH Intervention Research Grant MH-40279

Session II – 83

Effects of Olanzapine Vs. Haloperidol on Progression of Brain Pathomorphology in First Episode Schizophrenia

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Longitudinal neuroimaging studies of first episode schizophrenia have demonstrated morphological changes in cortical gray matter and ventricular volumes that have been suggested to reflect pathological processes of developmental maturation and/or illness progression. Although some studies have considered the potential role of treatment in either contributing to or preventing brain morphological changes, no study has examined the comparative effects of atypical and conventional antipsychotic drugs in a controlled long-term trial.

This study examined the effects of haloperidol and olanzapine on psychopathology, cognition and brain morphology in patients with schizophrenia and schizoaffective disorder in a multicenter randomized controlled trial under double blind conditions for 104 weeks. Patients were assessed with high resolution sMRI at baseline and after 12, 24, 52 and 104 weeks of treatment. All sMRIs underwent computer based morphometric analysis to determine volumes of specified ROIs at a centralized laboratory using validated methods with proven reliability.

167 (of 263) patients (mean age 24 yrs, 70% male) had baseline and at least one follow-up sMRI. We assessed group differences at the end of the acute phase (week 12) and at the end of 24, 52, and 104 weeks. For the acute phase data analysis we used the end-of-acute-phase week 12 volume as the response, with baseline volume as a covariate, adjusting for investigator, age, and gender. For total cerebral gray matter, we found the 12 week changes to least squares means ± standard error to be for haloperidol -10.60±2.39 while for olanzapine it was -0.26±2.15 ($P<0.001$). For lateral ventricular volume, the changes to least squares means (in the same model used for gray matter volume), to be for haloperidol 0.54±0.44 while for olanzapine it was -0.38±0.41 ($P<0.06$).

These results replicate prior studies that found progressive changes in brain morphology consistent with the hypothesized effect of illness progression that can be selectively attenuated by treatment with olanzapine. These and additional results, for the acute phase and 24, 52, and 104 week follow-up measurements, will be presented and discussed.

Source of Funding: Eli Lilly and Company

Session II – 84

A Naturalistic Outcome Study Comparing Clozapine and Olanzapine/Risperidone in a Statewide Treatment Resistant Population

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Background: This effectiveness study examines whether clozapine (the "gold-standard" treatment for refractory patients) is associated with better outcomes than other antipsychotic treatments in a population of severely ill state hospital inpatients.

Methods: Using the NKI Integrated Research Database (IRDB), we selected NYS Office of Mental Health patients diagnosed with schizophrenia or schizoaffective disorder who were prescribed a single antipsychotic medication (monotherapy) between 1/1/98 and 7/1/00 and starting between the 90th and 360th days of hospitalization. Two groups of patients were compared: Those prescribed clozapine [C], and those prescribed either olanzapine *or* risperidone [O/R].
The following outcome measures were examined at 180 days from start of the index regimen:

- 1. Switches from index regimen to another antipsychotic regimen (similar to the primary outcome criterion of the CATIE Schizophrenia study).
- 2. Discharges on index regimen.
- 3. Discharges on *any* medication regimen.

Results: 639 patients were included in the analysis (153 C, 486 O/R). Groups did not differ in terms of race, sex, length of prior hospitalization, or start date of index medication. Clozapine patients were slightly younger, were more likely to be diagnosed with schizoaffective disorder, to have had multiple prior hospitalizations, to have had a trial of clozapine during a prior hospitalization, and to have had more previous medication trials during the current hospitalization than were olanzapine/risperidone patients.

Olanzapine/risperidone patients were significantly more likely to be switched off their medication regimen than were clozapine patients (40.5% vs. 32.0%). There was no significant difference either in the percent of patients discharged on the index regimen (32.5% O/R vs. 35.9% C), or percent discharged overall (43.6% O/R vs. 44.4% C). The results were unchanged after controlling for demographic, diagnostic, and treatment history differences between the groups.

Conclusions: In this study, although clozapine patients were less likely to be switched off their medication regimen, they showed no difference in hospital discharge rate compared with patients receiving olanzapine/risperidone. This outcome is consistent with the effectiveness study by Essock, et al., which showed no difference in hospital discharge for patients assigned to clozapine versus usual care. The interpretation of these findings will be aided by future comparison of outcomes with first-generation antipsychotics and hospital readmission data.

Source of Funding: Maintenance of the database is supported by Eli Lilly and Co. and Pfizer, Inc.

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Session II – 85

Ziprasidone Negative Symptom Efficacy in Long-Term Clinical Trials

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Objective: We reviewed ziprasidone's efficacy in treating negative symptoms in long-term double-blind trials and in extension studies of patients switched to ziprasidone from other antipsychotics.

Methods: Changes in PANSS Negative subscale scores were evaluated in four randomized, double-blind studies of ziprasidone versus placebo (52 weeks), haloperidol (28 weeks), olanzapine (>6 months), and risperidone (52 weeks), using analysis of covariance (ANCOVA). In three open-label extension studies (≥215 days) evaluating improvement following switch to ziprasidone from conventional agents, olanzapine, or risperidone, changes in PANSS Negative subscale scores were analyzed using paired *t*-tests.

Results: Ziprasidone was superior to placebo (LOCF, $p<0.05$) in improving negative symptoms. Change in PANSS Negative subscale score was not significantly greater than haloperidol, but percentage of PANSS Negative responders (≥20% decrease) was higher ($P<0.05$). Ziprasidone's treatment effect was comparable to olanzapine's (95% CI: -2.3, 2.8) and risperidone's (95% CI: -3.2, 2.4). In the switch studies, improvement was observed for patients switched from conventional agents ($p<0.01$), olanzapine ($p<0.05$), and risperidone ($p<0.01$).

Conclusions: In long-term treatment of negative symptoms of schizophrenia, ziprasidone showed efficacy superior to placebo's and comparable to olanzapine's and risperidone's and a responder rate higher than haloperidol's. Significant long-term improvement in negative symptoms was also observed in patients switched to ziprasidone from other antipsychotics.

Source of Funding: Pfizer, Inc.

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Rapid Ziprasidone Switch Experience in a Texas Long-Term Care Facility

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Objective: This retrospective analysis examines clinical and pharmacoeconomic outcomes for rapid switch of patients to ziprasidone from other failed conventional and atypical antipsychotic therapy.

Methods: Data was reviewed for thirty-one patients with diagnoses of schizophrenia, psychosis (NOS), bipolar disorder, dementia, self-injurious behavior, or intermittent explosive disorder that had previously failed treatment with haloperidol, olanzapine, quetiapine, or risperidone due to following:

- Benztropine or other anti-EPS medication
- Risperidone up to 6 mg with no response
- Olanzapine up to 70 mg with no response
- Quetiapine up to 800 mg with no response

Patient experienced adverse effect such as significant weight gain, hyperglycemia, or lipid elevations

Rapid switch to ziprasidone was accomplished as follows:

- DC previous antipsychotic on day 1
- Begin oral ziprasidone 40 mg BID on day 1 x 3 days; then increase to 80 mg BID (Further increases to 240 mg was made if clinically necessary)
- Adjunctive medications (benzodiazepines, beta blockers) were utilized if necessary
- Follow-up ECG performed within two weeks of rapid switch

Results: Retrospective analysis of data revealed that 51% of patients converted via rapid switch tolerated therapy and are stabilized on 160 mg/day with no adverse effects. Moreover, one-third of converted patients required an increase in dose to 240 mg/day with no decompensation. Furthermore, 9% of patients required restarting their previous atypical treatment (all of these patients were on high dose olanzapine—median dose of 45 mg). Finally, another 9% of patients did not tolerate ziprasidone due to nausea/vomiting, somnolence, or lack of response. Review of QTc measurements indicated no values greater than 500 msec (a mean change of 6 msec) for patients converted to ziprasidone. Hence, rapid switch treatment was effective and tolerated by 84% of patients reviewed.

Conclusion: Patients on moderate doses of other conventional and atypical agents can be switched smoothly to ziprasidone. Furthermore, those individuals receiving olanzapine doses greater than 40 mg/day would benefit from a more gradual tapering. Finally, patients receiving olanzapine at doses greater than 40 mg/day or higher doses of another atypical agent will most likely require ziprasidone 240 mg/day to become stable. Economic impact of this switch is projected to have an annual cost avoidance of $93,227 for this long-term care facility.

Source of Funding: None

Session II – 87

Dose-Adjusted Olanzapine and Fluvoxamine Interaction: A Novel Therapeutic Strategy to Reduce Olanzapine Dose Requirements in Major Psychosis

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Background and Rationale: Schizophrenia is a common mental health problem with a life time prevalence of 1%. Despite the advances in pharmacotherapy in the past decade, many of the newer antipsychotic agents are not readily accessible in patients with major psychosis or in developing countries where the acquisition costs may be prohibitive. Olanzapine (OL) is an efficacious broad spectrum atypical antipsychotic with a favorable neurological safety profile. In theory, OL therapeutic dose requirements may be reduced during concurrent treatment with inhibitors of drug metabolism. Earlier in vitro studies suggest that CYP1A2 may contribute to formation of the metabolite N-desmethyl-olanzapine (des-OL). The present prospective study tested the hypothesis that OL steady-state doses can be significantly decreased by co-administration of a low subtherapeutic dose of fluvoxamine (FV: a potent inhibitor of CYP1A2) while maintaining a stable pharmacokinetic exposure and clinical response to OL.

Methods: Smoker patients with major psychosis (N=10 males) (age: 51.2±6.4 yrs) (mean±SD) and receiving chronic OL treatment for at least the past 4 months were evaluated for steady-state plasma concentrations of OL and des-OL, severity of psychosis (BPRS), standard metabolic indices (blood glucose, cholesterol, triglycerides and HDL) and body weight. Subsequently, OL dose was reduced by 25% to 33% from 17.5±4.2 mg/d to 13.0±3.3 mg/d and a subclinical dose of FV (25 mg/d, po) was added to regimen. Patients were re-evaluated at 2, 4 and 6 weeks during OL-FV co-treatment. Compliance to drug treatment was closely monitored by clinical staff. Smoking habits (26 cigs/d ± 9.1) remained unchanged throughout the 6 week study period.

Results: There was no significant change in OL concentration after dose reduction in the presence of FV ($p>0.05$). A modest improvement in antipsychotic response was noted at 6 weeks (BPRS=30.0±4.7) compared to baseline (34.7±5.9) ($p<0.05$). Des-OL/OL metabolic ratio decreased by 45% from 0.45±0.20 at baseline to 0.25±0.11 at week 6, suggesting inhibition of CYP1A2 by FV ($p<0.05$). The OL-FV combination was well-tolerated. There was no significant change in metabolic indices or body weight at 6-weeks ($p>0.05$).

Conclusions: This prospective study suggests that a 26% reduction in mean OL therapeutic dose requirement can be achieved by co-administration of a subclinical oral dose of FV (25 mg/d). We found that this intervention did not cause any appreciable change in OL plasma levels while maintaining a stable antipsychotic response throughout the study. From a health economics and policy point of view, these data provide an empirical basis for long-term prospective evaluations to optimize OL treatment and enhance access to atypical antipsychotics in patients with major psychosis.

Source of Funding: Supported by a grant from the West Coast College of Biological Psychiatry

Session II – 88

Peripheral Oxytocin Release Among Depressed, Remitted, and Control Females: Pilot Findings

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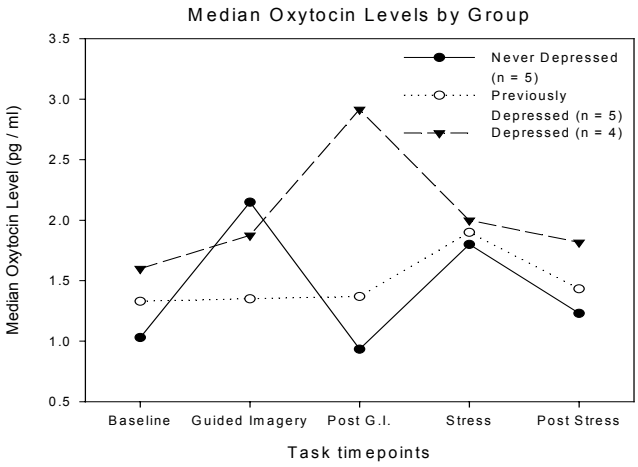
Background: Post-pubertal females are twice as likely as males to experience a lifetime history of major depression, and are particularly likely to become depressed when faced with interpersonal life stress. We have theorized that women's sensitivity to interpersonal life stress is mediated, in part, by the hypothalamic neurohormone, oxytocin. Oxytocin is known to play a key role in female reproductive processes. A growing body of animal research indicates that oxytocin also facilitates affiliative behaviors and modulates hypothalamic-pituitary-adrenal responses to stress in mammalian females.

Methods: The current pilot study was developed to stimulate, measure and compare peripheral oxytocin release and basal oxytocin concentrations between groups of currently depressed (n=4), previously depressed (n=5) and never depressed (n=5) women. Plasma levels of oxytocin were assessed over three 20-minute rest periods and two 10-minute laboratory induction tasks using a peripheral sampling frequency of every 5 minutes accomplished via in-dwelling catheter. Laboratory tasks included an affiliation-focused guided imagery task and a speech stress task.

Results: As expected, never-depressed women displayed low and relatively stable levels of oxytocin during rest periods, contrasted by spikes of oxytocin release during laboratory induction tasks. Depressed and previously depressed women displayed a less consistent pattern of release, with currently depressed subjects showing a trend toward increased oxytocin release during the rest period following the affiliation-focused imagery task (Kruskal-Wallis $x^2 = 5.19$, df = 2, p = .07). See Figure, below.



Notably, mean oxytocin levels during this rest period were significantly associated with self-reports of reduced social support (Spearman $r = -0.57$, $p < .05$) and greater behavioral inhibition (Spearman $r = .63$, $p < .05$), and were marginally associated with self-reported anxiety (assessed with the BAI and the anxious arousal subscale of the MASQ, p's = .06).

Conclusion: Preliminary evidence supports the notion that depressed women may display dysregulation in peripheral oxytocin release. These findings warrant further investigation.

Source of Funding: National Institute of Mental Health

Session II – 89

High-Dose Ziprasidone Is Associated with Marginal Additional QT_c Increase

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Objective: To characterize QT_c effects of oral ziprasidone and haloperidol at three steady-state dose levels.

Methods: After tapering and washout of existing antipsychotic therapy, subjects with schizophrenia or schizoaffective disorder were randomized to escalating doses of ziprasidone (40, 160, and 320 mg/day) or haloperidol (2.5, 15, and 30 mg/day) administered over 16 days to attain steady-state dose levels. ECGs were collected at baseline (drug-free condition) and during study drug administration on steady-state days 4, 10, and 16, at estimated T_{max} and 1 hour before and after. Samples for pharmacokinetic measurements were collected at estimated T_{max}, and telemetry was performed throughout the high-dose period.

Results: Mean ziprasidone concentrations (n=25) increased ~6-fold across the 40-320 mg/day dose range, reaching 327 ng/mL at the 320 mg/day dose level. Mean ΔQT_c from baseline were 4.5 msec at 40 mg/day, 19.5 msec at 160 mg/d, and 22.5 msec at 320 mg/day. For haloperidol (n=23), mean ΔQT_c were –1.2, 6.6, and 7.2 msec at the three respective dose levels. No telemetric abnormalities or $QT_c \geq 500$ msec were observed.

Conclusions*:* At twice the recommended daily dose, oral ziprasidone showed marginal QT_c increase from 160 mg/day, with no significant cardiovascular symptoms or $QT_c \geq 500$ msec.

Source of Funding: Pfizer, Inc.

Session II – 90

Absence of an Association Between Fluvoxamine and Bleeding-Related Adverse Events

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Objective: To determine the association between bleeding-related adverse events (BRAE) and fluvoxamine (Luvox® Tablets) or placebo treatment, administered alone or concomitantly with medications associated with BRAE.

Method: A retrospective analysis was conducted with data from double-blind, placebo-controlled studies. BRAE were identified by COSTART terms. Exposure was expressed as person-years of exposure, risk as the number of BRAE divided by the number of patients and rate as the number of BRAE divided by person-years of exposure.

Results: A total of 68 trials with 5984 patients were identified. Fluvoxamine exposure totaled 645 person-years; placebo exposure was 237 person-years. Approximately 2% of both groups (N = 76 and 44, respectively) reported BRAE. Demographics and concomitant medication (CM) usage are in Table 1. The 95% confidence intervals (CI) for the risk and rate of BRAE revealed an overlap between the two groups (Table 2). Fluvoxamine and placebo patients taking CM reported the majority of BRAE (88% and 82%, respectively). Three serious BRAE (2 fluvoxamine, 1 placebo) and 11 dropouts from BRAE (6 fluvoxamine, 5 placebo) occurred. Most BRAE were menstrual difficulties.

Table 1. DEMOGRAPHICS AND CM USAGE

	Fluvoxamine N (%)	Placebo N (%)
Female	2533 (64)	1254 (62)
Total	3955	2029
BRAE Related CM		
Anticoagulants	8 (<1)	1 (<1)
Antiplatelets	12 (<1)	3 (<1)
NSAIDS	816 (21)	540 (27)*
Steroids	81 (2)	79 (4)*
Not BRAE-related	2627 (66)	1282 (63)
Unknown	97 (2)	75 (7)
No CM	1075 (27)	580 (29)

*= $p<0.001$ (chi-square)

Table 2. RISK AND RATE OF BRAE – 95%CI

	Fluvoxamine	Placebo
Risk	0.019 (0.015 – 0.024)	0.022 (0.016 – 0.029)
Rate	0.118 (0.094 – 0.143)	0.185 (0.138 – 0.241)

Conclusions: The overall incidence of BRAE associated with fluvoxamine or placebo use was low (approximately 2%). No meaningful difference in risk of BRAE was apparent. Only minimal overlap was noted in the 95% CI for the rate of total BRAE (fluvoxamine 0.09 – 0.14 vs. placebo 0.14 – 0.24) suggesting more BRAE were reported by placebo-treated patients.

Source of Funding: Solvay Pharmaceuticals, Inc.

Session II – 91

Antipsychotic Medication Treatment and New Prescriptions for Insulin and Oral Hypoglycemics

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Objective: To detect the increase in risk of diabetes mellitus from exposure to atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine) compared to typical antipsychotics.

Methods: Using a retrospective case-control study design, odds ratios were calculated regarding exposure to different antipsychotics. Cases (patients receiving a new prescription of insulin or an oral hypoglycemic as a proxy for diabetes mellitus) and controls were identified for calendar years 1997 and 2000 using a database containing drug prescription information from the in-patient facilities operated by the New York State Office of Mental Health. Ten controls for each case were matched by length of observation period, age group, and ethnicity. Among 11,579 patients in 1997 and 9,622 patients in 2000, 5,751 and 4,923, respectively, met our entry criteria of being hospitalized at least 60 days, prescribed antipsychotic medication, and not prescribed anti-diabetic medication during the three prior calendar years.

Results: Incident cases increased from 39 out of 5751 (0.68%) in 1997 to 58 out of 4923 (1.18%) in 2000. In the year 2000, statistically significant elevations in risk were observed for patients receiving atypical antipsychotics as a group compared to those receiving typical antipsychotics (OR=3.15, 95% CI=1.12-8.91), with the largest risk seen for clozapine (OR=7.61, 95% CI=2.36-24.55). Odds ratios for olanzapine, risperidone and quetiapine were elevated, but the confidence intervals overlapped considerably, preventing meaningful attempts to compare these agents amongst each other. In 2000, patients prescribed clozapine received plasma glucose tests more frequently than patients prescribed other antipsychotics.

Conclusions: In 2000, exposure to atypical antipsychotics as a group increased the risk of developing diabetes mellitus, as defined by receiving a new prescription for an anti-diabetic agent. Risk was highest with clozapine and may have been related to increased surveillance for diabetes mellitus. A significant limitation is the small number of incident cases. Future analyses will focus on combining consecutive calendar years in order to increase statistical power.

Source of Funding: The design and conduct of the study, the collection, analysis, and interpretation of the data, and the preparation, review, and approval of the manuscript was done independently by the authors, with no input from any of the pharmaceutical companies.

Session II – 92

A Double Blind Trial of Olanzapine for Reducing Cue-Elicited Cocaine Craving in Schizophrenia

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Background/Objective: Recent research suggests that individuals with schizophrenia and cocaine-dependence have a great deal of persistent self-report craving and cue-elicited craving that plays a role in the high substance abuse relapses common in this population (Carol et al, 2001; Smelson et al, 2002). These studies highlight the need to develop pharmacological and psychosocial anticraving interventions to assist in treatment. Open label studies suggest that atypical neuroleptics may be useful for treating schizophrenia and cocaine dependence (Smelson et al, 2002).

Methods: We conducted a six-week double-blind trial comparing olanzapine and haloperidol for reducing craving and relapses in individuals diagnosed with schizophrenia and cocaine dependence. Subjects were administered a weekly cue-exposure procedure to prime patients with cocaine related cues in a laboratory and study the anticraving effects.

Results: Individuals treated with olanzapine (n=16) showed significantly less cue-elicited craving on the energy (.01) and sick (.05) dimensions of craving and 12.5% had a positive urine toxicology screening for an illicit substance compared to 40% of those in the haloperidol group (n=15). This difference in craving reduction was even greater for the study completers.

Conclusions: Olanzapine appears to be an effective adjunctive treatment for decreasing cocaine craving and preventing relapses among cocaine dependent schizophrenics.

Source of Funding: This study was supported by an investigator-initiated trial from Eli Lilly.

Session II – 93

Naltrexone Does Not Impact on Fluoxetine/Norfluoxetine Plasma Concentration in Depressed Alcoholics

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Background: The utility of combined pharmacotherapy of fluoxetine and naltrexone in the treatment of comorbid major depression and alcohol dependence have been previously reported by our group{Salloum, Cornelius, et al. 1998 #1010}. It is unclear, however, whether there are any interactions between fluoxetine and naltrexone when given together. To date, there are neither reports examining the serum concentrations of fluoxetine and its active metabolite, norfluoxetine, and the impact of additional naltrexone dosing on blood concentrations, nor are there data on the potential usefulness for routine therapeutic drug monitoring among depressed patients with co-occurring alcoholism. Fluoxetine, dispensed as a racemate of R- and S- fluoxetine (FL), is metabolized by the liver to R- and S-norfluoxetine (NFL). These S and R enantiomers have differential rates of hepatic metabolism, and may also have different neuropharmacological affinities to neurotransmitters system. It is unclear how concurrent treatment with naltrexone impacts on their individual metabolism, and whether it may have differential implication for monitoring of treatment and drug toxic effects.

The aim of this study is to examine whether naltrexone impacts on the plasma concentrations of fluoxetine and norfluoxetine, and also to explore whether fluoxetine/ norfluoxetine plasma concentrations predict change in alcohol use among these patients.

Methods: The sample consists of 43 patients participating in an ongoing clinical trial evaluating the efficacy of * fluoxetine (dose range 20-60mg/day) * naltrexone hydrochloride (dose 50 mg/day) in the treatment of major depression with comorbid alcoholism. We used validated chiral methods (Perel & Assoc., Cli. Pharmacol. Ther. 59:213, 1996) to measure plasma concentrations for R- & S- Fuoxetine and R- & S-Norfuoxetine in 175 samples. We used one-way ANOVA to examine whether the plasma concentrations for R- & S-Fuoxetine and R- & S-Norfuoxetine differ between fluoxetine + naltrexone compared to fluoxetine + placebo groups on weeks 1, 3, 6, 12, and 20. Furthermore, using a Mixed effects model, we examined whether steady state fluoxetine/ norfluoxetine plasma concentrations predict change in alcohol use among these patients.

Results & Conclusion: The results of this study showed that there were no statistically significant differences between the two groups on plasma concentrations for R- & S-Fluoxetine and R- & S-Norfluoxetine. Furthermore, the Mixed effects model revealed that there was an interaction effects between group membership and total fluoxetine/norfluoxetine plasma concentration. High levels of total fluoxetine/norfluoxetine plasma concentrations in the naltrexone group were associated with low alcohol use over time. On the other hand, low levels of total fluoxetine/norfluoxetine plasma concentration in the naltrexone placebo group was associated with high alcohol consumption ($F=3.88$, $p=0.052$). These results indicate that naltrexone does not appear to impact on fluoxetine/norfluoxtine metabolism. Further, total fluoxetine/norfluoxetine concentrations appear to correlate with alcohol use in the naltrexone treated group.

Source of Funding: This work was supported by USPHS Grants R01AA11929; R01AA13370, and a VA VISN4 MIRECC grant.

Session II – 94

AN OPEN TRIAL OF THE SAFETY AND EFFICACY OF MIRTAZAPINE IN CHILDREN AND ADOLESCENTS WITH SOCIAL PHOBIA

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Background*:* Pediatric social phobia can be debilitating. Estimating the effects of potential treatments is important.

Methods: Eighteen subjects, 8 to 17 years old, with DSM-IV Social Phobia underwent 8-weeks of open treatment with Mirtazapine up to the lesser of 0.8 mg/kg/day or 45 mg/day. Starting dose was 15mg. The primary outcome measure was the Clinical Global Impressions Scale for Social Phobia (CGI-SP). Adverse events and Complete Blood Counts (CBC) were monitored.

Results: Fifty-six% (10/18) were responders (CGI-SP-Improvement $\leq$ 2, much or very much improved) and 17% (3/18) achieved remission (final CGI-SP-Severity score $\leq$ 2 and CGI-SP-Improvement score $\leq$ 2). Mean CGI-SP-Severity scores decreased 1.06$\pm$1.06 (t_{17}=4.242, p=0.001). This decrease reached significance versus baseline at week two on Mirtazapine. The mean decrease in the Liebowitz Social Anxiety Scale (LSAS) total score was 43$\pm$36% (t_{17}=5.188, p<0.001). The LSAS Anxiety and Avoidance subscales had mean decreases of 41$\pm$31% and 46$\pm$42% respectively (t_{17}=5.687, p<0.001; t_{17}=4.575, p<0.001). The mean final daily dosage of Mirtazapine was 29±12 mg/day (0.5$\pm$0.2 mg/kg/day). Twenty-two% (n=4) discontinued due to adverse effects. They were mild in 5.6% (n=1) and moderate in 16.7% (n=3) of subjects, and resolved within a day in all cases. Mean weight gain was 3.3$\pm$2.6 kg. This resulted in an increase in weight percentile based on height and age from 62$\pm$24 at baseline to 69$\pm$24 (t_{17}=3.842, p=0.001).

Conclusions: Mirtazapine treatment was associated with significant improvement in social phobia and was well tolerated with adverse events being mild to moderate in nature. Fifty-six% responded. Seventeen% had complete remission of symptoms.

Source of Funding:
Unrestriced educational grant from Organon Inc.

SESSION II - 95

DISCRIMINATING ATTENTION DEFICIT HYPERACTIVITY DISORDER THROUGH OBJECTIVE MEASURES OF MOTION AND ATTENTION

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Objective: The present study was designed to test if objective measures of motion and attention in a depressed population could distinguish children and adolescents with Major Depressive Disorder (MDD) from those with a comorbid diagnosis of MDD and Attention Deficit Hyperactivity Disorder (ADHD). Past studies have shown that these objective measures have the ability to discriminate between normal children and those who have ADHD.

Methods: Thirty-four subjects, medication free and ages 7 to 17, meeting DSM-IV criteria for MDD or MDD plus ADHD, as determined by the Kaufman Schedule for Affective Disorders and Schizophrenia – Present and Lifetime (K-SADS-PL), performed a computer-generated continuous performance task called the McLean Motion and Attention Test (MMAT, previously called OPTAx). The SNAP-IV also significantly differentiated the two groups. Objective measures of attention were obtained by performance results while an infrared optical motion sensor obtained objective measures of motion.

Results: Subjects with MDD alone and those with comorbid MDD and ADHD significantly differed on 5 out of the 6 measures of motion tested by the MMAT indicating greater movement, area displaced, temporal scaling and decreased immobility on the task by the comorbid group (all independent t-tests with $p < .05$). In addition, the two groups significantly differed on 5 out of the 6 CPT measures of attention tested by the MMAT (accuracy, omission and commission errors, variability, and response inconsistency – all $p < .05$) with the comorbid group having the most attention-related errors. Both groups had comparable CDRS scores (mean = 72.6 ± 7.4 for MDD and 70.1 ± 7.0 for the comorbid group).

Conclusion: Findings suggest that tools, such as the MMAT, which objectively measure motion and attention, are useful instruments in helping to identifying ADHD even among children and adolescents with comorbid MDD and ADHD in comparison to MDD alone. Thus, the test's usefulness in detecting ADHD in a normal population can be extended to a depressed population as well. The addition of such tools, which provide independent and objective means of evaluating psychiatric disorders, may be valuable to clinicians who incorporate the instruments into their standard diagnostic batteries. Follow-up work is in the process of assessing the impact of pharmacological intervention on these scores.

Source of Funding: National Institutes of Mental Health (NIH-RO1-MH39188-09), Graham Emslie (P.I.),

SESSION II - 96

Functional Brain Magnetic Resonance Imaging (fMRI) Study of Problem-Solving and Hope in Healthy Volunteers

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Introduction: Using PET technology, *reduced* prefrontal cortical brain metabolism was recently reported in suicide attempters (versus non-attempters) following the administration of a serotonin-releasing agent (fenfluramine). Neuropsychological tests in depressed suicide attempters versus non-attempters have identified significantly *reduced* problem –solving / strategic thinking / verbal fluency in depressed suicide attempters, suggesting that frontal cortical dysfunction is associated with depression with suicidal features. We used an fMRI executive reasoning and future-thinking paradigm in healthy volunteers to analyse brain circuits that may be involved in thought processes related to problem-solving and future thinking as a model for studying the suicidal brain.

Methods: Nine right-handed male volunteers were scanned during activation and rest periods of cognitive tasks of executive functioning and Future Thinking, using fMRI (1.5T imaging system,). Data were converted from DICOM to Analyze format and analysed using statistical parametric mapping (SPM99, UK) implemented in MATLAB (Mathworks Inc, USA).

Results: During the silent word generation task, significant blood oxygenation level dependent (BOLD) signal increases were seen when the activation periods were contrasted with rest periods. The left cerebrum and frontal lobe showed an increase in signal intensity, including previously reported areas such as including dorsolateral prefrontal cortex, orbitofrontal cortex, Broca's speech area and the temporal cortex. The left hemisphere was activated to a greater extent than the right. Discrete frontal brain activity was visualised in response to the Future Thinking Test (FTT) where greater areas of cortical activation were observed in response to FTT positive versus FTT negative using random effects analysis.

Conclusions: Depression, especially when accompanied by suicidal features is a major health problem in Ireland. Few studies (and none in Ireland to date) have focussed on the biologic aetiology / brain mechanisms involved in the manifestation of suicidal features during a depressive episode. Our FTT brain imaging data in healthy volunteers suggest that brain circuits associated with cognitive processes of Hope versus Despair are balanced, with greater brain activation generated for positive events in healthy subjects.

Source of Funding: Mater Hospital College for Post-graduate Education and Research, and Irish Health Research Board (Summer Student Award).

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